federal register

Thursday,
September 8, 1988

Part IV

Department of Health and Human Services

Health Care Financing Administration

Medicare Program; Withdrawal of Coverage of Single Photon Absorptiometry and Radiographic Absorptiometry and Radiographic Absorptiometry (Photodensitometry) and Continued Noncoverage of Dual Photon Absorptiometry; Notice

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Health Care Financing Administration

[BERC-446-PN]

Medicare Program, Withdrawal of Coverage of Single Photon Absorptiometry and Radiographic Absorptiometry (Photodensitometry) and Continued Noncoverage of Dual Photon Absorptiometry

AGENCY: Health Care Financing Administration (HCFA), HHS.

ACTION: Proposed notice.

SUMMARY: This notice announces the Medicare program's intent to withdraw Medicare coverage (including coverage under the End Stage Renal Disease (ESRD) program) for single photon absorptiometry, and radiographic absorptiometry (photodensitometry) for measuring bone mineral density for either diagnostic purposes or as a guide to treatment, and to continue noncoverage of dual photon absorptiometry.

DATE: Comments will be considered if we receive them at the appropriate address, as provided below, no later than 5:00 p.m. on November 7, 1988.

ADDRESS: Mail comments to the following address: Health Care Financing Administration, Department of Health and Human Services, Attention: BERC-446-PN, P.O. Box 26676, Baltimore, Maryland 21207.

If you prefer, you may deliver your comments to one of the following addresses:

Room 309-G, Hubert H. Humphrey Building, 200 Independence Ave., SW., Washington, DC, or

Room 132, East High Rise Building, 6325 Security Boulevard, Baltimore, Maryland.

In commenting, please refer to file code BERC-446-PN. Comments received timely will be available for public inspection as they are received, generally beginning approximately three weeks after publication of a document, in Room 309-G of the Department's offices at 200 Independence Ave., SW., Washington, DC, Monday through Friday of each week from 8:30 a.m. to 5:00 p.m. (phone: 202-245-7890).

FOR FURTHER INFORMATION CONTACT: Barton McCann, M.D., (301) 594-9370.

SUPPLEMENTARY INFORMATION:

I. Background

Administration of the Medicare program is governed by the Medicare statute, title XVIII of the Social Security Act (the Act). The Medicare law provides coverage for broad categories of benefits, including inpatient and outpatient hospital care, skilled nursing facility (SNF) care, home health care, and physicians' services. It places general and categorical limitations on the coverage of the services furnished by certain health care practitioners, such as dentists, chiropractors and podiatrists, and it specifically excludes some categories of services from coverage, such as cosmetic surgery, personal comfort items, custodial care, routine physical checkups, and procedures that are not reasonable and necessary for diagnosis or treatment. The statute also provides direction as to the manner in which payment is made for Medicare services, the rules governing eligibility for services, and the health, safety and quality standards to be met by institutions providing services to Medicare beneficiaries.

The Medicare law does not, however, provide an all-inclusive list of specific items, services, treatments, procedures, or technologies covered by Medicare. Thus, except for the examples of durable medical equipment in section 1861(n) of the Act, and some of the medical and other health services listed in sections 1861(s) and 1862(a) of the Act, the statute does not specify medical devices, surgical procedures, or diagnostic or therapeutic services that should be covered or excluded from coverage.

The intention of Congress, at the time the Medicare Act was enacted in 1965, was that Medicare would provide health insurance to protect the elderly or disabled from the substantial costs of acute health care services, principally hospital care. The provision was designed generally to cover services ordinarily furnished by hospitals, SNFs, and physicians licensed to practice medicine. Congress understood that questions as to coverage of specific services would invariably arise and would require a specific decision of coverage by those administering the program. Thus, it vested in the Secretary the authority to make those decisions. Specifically, section 1862(a)(1)(A) of the Act prohibits payment for any expenses incurred for items or services "which are not reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member."

We have interpreted this statutory provision to exclude from Medicare coverage those medical and health care services that are not demonstrated to be safe and effective by acceptable clinical evidence. Effectiveness in this context is defined as the probability of benefit to individuals from a medical technology for a given medical problem under actual conditions of use. In day-to-day medical practice, physicians diagnose and treat clinical conditions following their performance of history and physical examinations and their interpretations of a variety of diagnostic tests and procedures. To be of value to the physician in confirming the presence or absence of a given disease, the information obtained from any diagnostic test or procedure must be of sufficient accuracy to establish or rule out the presence of that disease. Likewise, for established diagnoses, the test or procedure must be of sufficient precision to allow the physician to accurately monitor the patient's response to treatment. Payment may not be made under Medicare for any diagnostic test or procedure that is not accurate or precise, since such a test cannot be considered "reasonable and necessary for the diagnosis or treatment of illness or injury". While medical procedures may prove to be efficacious in a research setting, under ideal circumstances (that is, controlled environment, scientifically trained users, optimally functioning equipment, etc.) their efficacy may not extend to less controlled settings. On April 29, 1987, we published a notice in the **Federal Register** (52 FR 15560) that describes the process we use in reaching coverage decisions. That notice includes a discussion of our reliance on the Office of Health Technology Assessment (OHTA) in the Public Health Service (PHS) for medical advice.

The Medicare program currently covers single photon absorptiometry, radiographic absorptiometry (photodensitometry), and bone biopsy for measuring bone mineral density. Dual photon absorptiometry currently is not covered.

Bone mineral density studies are used to diagnose diseases of the bone and to evaluate the responses of bone diseases to treatment. The studies assess bone mass or density associated with such diseases as osteoporosis, osteomalacia, and renal osteodystrophy. Various methods of measurement may be used to diagnose bone disease and monitor the response to treatment, including, bone biopsy, radiographic absorptiometry (photodensitometry), and single and dual photon absorptiometry.

A bone biopsy is an invasive surgical procedure. A small sample of bone (usually from the hip) is removed, generally by a biopsy needle. The biopsy sample is then examined histologically, and provides a qualitative measurement of the bone mineral

content of the trabecular bone. This procedure is used primarily to differentiate osteomalacia from osteoporosis. Bone biopsy is covered under Medicare when used for the qualitative evaluation of bone no more than four times per patient, unless special justification is given. When used more than four times on a patient, bone biopsy may leave a defect in the pelvis and produce some patient discomfort.

Radiographic absorptiometry (photodensitometry) is a noninvasive radiological procedure that attempts to assess bone mass by measuring the optical density of extremity radiographs with a photodensitometer, usually with a reference to a standard density wedge placed on the film at the time of exposure. This procedure provides a quantitative measurement of the bone mineral of cortical bone, and is used for monitoring gross bone change.

Radiographic absorptiometry (photodensitometry) was covered in 1975 at the recommendation of the Bureau of Health Insurance's (predecessor to HCFA) in-house medical consultants based on the limited medical information available at that time. This decision was made prior to the inception of the HCFA Physicians Panel and OHTA review and assessment process. Since that time additional studies have been conducted, with the result that the available evidence as set forth in current medical literature no longer supports Medicare's coverage position.

Single photon absorptiometry is a non-invasive radiological technique that measures absorption of a monochromatic photon beam by bone material. The device is placed directly on the patient, uses a low dose of radionuclide, and measures the mass absorption efficiency of the energy used. It provides a quantitative measurement of the bone mineral of cortical and trabecular bone, and is used in assessing an individual's treatment response at appropriate intervals. Single photon absorptiometry has been covered under Medicare when used in assessing changes in bone density of patients with osteodystrophy or osteoporosis when performed on the same individual at intervals of six to 12 months.

Single photon absorptiometry was covered under Medicare based on the advice and recommendation of the Office of Health Research, Statistics, and Technology (OHRST), PHS on September 10, 1982. OHRST stated that while no single currently available technique was entirely satisfactory for assessing either the degree or type of bone disease in individual patients, they recommended that single photon absorptiometry be covered under Medicare because "There does *appear* to be evidence to support the clinical effectiveness of photon absorptiometry * * *" Since that time additional studies have been conducted, with the result that the available evidence as set forth in current medical literature no longer supports Medicare's coverage position.

Dual photon absorptiometry is a noninvasive radiological technique that measures absorption of a dichromatic beam by bone material. This procedure is not covered under Medicare because it is still considered to be in the investigational stage.

The issue of the safety and effectiveness of dual photon absorptiometry was considered by the HCFA Physicians Panel on January 11, 1984. The HCFA Physicians Panel is an internal organization composed of physicians and other health professionals in HCFA's Central Office and their counterparts from PHS, which meets approximately once every six to eight weeks. At that time, the Panel recommended that HCFA refer the issue to PHS for its review with specific direction to OHTA to report back to HCFA after it had reviewed the data presented at a Consensus Conference on Osteoporosis at the National Institutes of Health (NIH) in April of 1984.

OHTA reported on the NIH conference at the Panel meeting held May 15, 1984. The NIH conference was unable to reach a consensus on the effectiveness in the clinical setting of any of the currently available tests for studying bone mineral density. The discussion generated by this information led HCFA to question whether these techniques were medically necessary, given the current state of therapy for osteoporosis. A major conclusion of the NIH conference was that while there are a number of promising treatments available for osteoporosis, there was no single treatment available to either prevent or cure the condition. The Panel then recommended that OHTA be requested to do a full assessment of the effectiveness of all types of bone mineral density studies.

On June 1, 1984, we requested that OHTA assess the issue of the safety and effectiveness of all currently used bone mineral density studies—radiographic absorptiometry (photodensitometry), single photon absorptiometry, dual photon absorptiometry, and computerized tomography (CT) scans. In a **Federal Register** notice published October 26, 1984, OHTA announced that it was coordinating an assessment of what is known of the safety, clinical effectiveness, and use of bone mineral density studies. During its assessment, OHTA solicited information and advice from other PHS components (such as the Food and Drug Administration and NIH), consulted directly with concerned medical specialty groups and professional organizations to determine whether a consensus exists within the medical community concerning the safety and effectiveness of bone mineral density studies, and researched and analyzed published medical and scientific literature and findings of all relevant studies and reports. On December 31, 1986, OHTA recommended that we not cover single photon absorptiometry under Medicare (including the ESRD program), and continue to deny Medicare coverage of dual photon absorptiometry. On September 22, 1987, OHTA recommended that we not cover radiographic absorptiometry (photodensitometry) under Medicare.

According to the OHTA assessment, the use of radiographic absorptiometry (photodensitometry), single photon absorptiometry, and dual photon absorptiometry for diagnosing bone loss or monitoring effectiveness of treatment is unproven. Currently, there is a lack of medical evidence supporting their effectiveness as either diagnostic tools or methods of monitoring treatments for bone disease when used outside the research setting. Because of significant variation among observers in obtaining measurements, and because measurements by the same observer at different times vary to a considerable degree, the accuracy of these measurements must be considered open to question. Moreover, it has not been determined which site or sites are best suited for measurement. When used as a guide to monitoring treatment response the degree of change in bone density expected is smaller than the precision error of the devices themselves, thereby making such measurements unsuitable for this purpose. OHTA has advised that radiographic absorptiometry (photodensitometry), single photon absorptiometry, and dual photon absorptiometry need to undergo further clinical investigation before being recommended for general clinical use. OHTA has, therefore, concluded that the available clinical and scientific evidence does not support the effectiveness in a day-to-day clinical setting, of radiographic absorptiometry (photodensitometry), single photon absorptiometry, and dual photon absorptiometry in measuring bone mineral density for either diagnostic or treatment monitoring purposes.

HCFA has received recently comments form clinicians and others challenging the OHTA assessments of the effectiveness of radiographic absorptiometry (photodensitometry), single photon absorptiometry, and dual photon absorptiometry in measuring bone mineral density for either diagnostic or treatment monitoring purposes that may have a substantial, credible basis. These comments will be available for public inspection during the comment period for this notice and will be addressed in the final notice if we proceed with publishing one.

OHTA is currently assessing the safety and effectiveness of computerized tomography (CT) scans when used to measure bone mineral density.

II. Provisions of the Proposed Notice

We propose to exclude radiographic absorptiometry (photodensitometry) and single photon absorptiometry for measuring bone mineral density from Medicare coverage (including coverage under the ESRD program) for either diagnostic purposes or as a guide to treatment, and to continue noncoverage of dual photon absorptiometry.

The provisions of this notice would not affect any existing Medicare regulations. However, they would affect the following manual instructions:

- Coverage Issues Manual—Section 50–17, paragraph A, Laboratory Tests—CRD Patients; and Section 50–44, Bone Mineral Density Studies;
- Renal Dialysis Facility Manual—Section 240.3, paragraph D, Laboratory Tests;
- Hospital Manual—Section 238.2, paragraph D.3., Institutional Dialysis Services Furnished to CAPD Patients—Laboratory Tests;
- Intermediary Manual—Section 3172.3, Laboratory Tests for Hemodialysis, Intermittent Pertioneal Dialysis (IPD) and Continuous Cycling Pertioneal Dialysis (CCPD) Included in the Composite Rate—Guidelines for Separately Billable Tests for Hemodialysis, IPD, and CCPD; and
- Carriers Manual—Section 2231.3, Support Services and Supplies Furnished to Home CAPD Patients, paragraph D.3., Laboratory Tests; and Section 4270, paragraph C.3., Guidelines for Separately Billable Tests for Hemodialysis, IPD, and CCPD.

III. Appendices

We have included as appendices to this notice the following OHTA assessments of single and dual photon absorptiometry.

APPENDIX I—Public Health Service Reassessment of Single Photon Absorptiometry for Measuring Bone Mineral Density—1986

APPENDIX II—Public Health Service Assessment of Dual Photon Absorptiometry for Measuring Bone Mineral Density—1986

APPENDIX III—Public Health Service Assessment of Radiographic Absorptiometry for Measuring Bone Mineral Density—1987

IV. Regulatory Impact Statement

Executive Order (E.O.) 12291 requires us to prepare and publish an initial regulatory impact analysis for any proposed notice that meets one of the E.O. criteria for a "major rule"; that is, that would be likely to result in: An annual effect on the economy of $100 million or more; a major increase in costs or prices for consumers, individual industries, Federal, State, or local government agencies, or geographic regions; or significant adverse effects on competition, employment, investment, productivity, innovation, or on the ability of United States-based enterprises to compete with foreign-based enterprises in domestic or export markets. In addition, we generally prepare an initial regulatory flexibility analysis that is consistent with the Regulatory Flexibility Act (RFA) (5 U.S.C. 601 through 612), unless the Secretary certifies that a proposed notice such as this would not have a significant economic impact on a substantial number of small entities.

Although radiographic absorptiometry has been covered since 1975, the first year for which Medicare coverage was available for single photon absorptiometry was 1985. The limited data available to us show the total 1985 Medicare charges for both procedures were significantly less than $1 million. This proposal would affect those clinics and other facilities that are offering this testing in two ways: first, they would lose Medicare revenue, and second, our coverage decision may affect other payers (such as, third parties) and their beneficiaries. Nonetheless, we believe the economic impact of this notice would not be significant.

For these reasons, we have determined that a regulatory impact analysis is not required. Further, we have determined and the Secretary certifies that this proposed notice would not have a significant economic impact on a substantial number of small entities, and we have therefore not prepared a regulatory flexibility analysis.

V. Response To Comments

Because of the large number of comments we receive on proposed notices, we cannot acknowledge or respond to them individually. However, in preparing the final notice, we will consider all comments received timely and respond to the major issues in that notice.

VI. Collection Of Information Requirements

This notice contains no information collection requirements. Consequently, this notice need not be reviewed by the Executive Office of Management and Budget under the authority of the Paperwork Reduction Act of 1980 (44 U.S.C. 3501 *et seq.*).

(Sec. 1862(a) of the Social Security Act (42 U.S.C. 1395y(a)))

(Catalog of Federal Domestic Assistance Program No. 13.773, Medicare Hospital Insurance and No. 13.774, Supplementary Medical Insurance)

Dated: February 26, 1988.

William L. Roper,

Administrator, Health Care Financing Administration.

Approved: April 9, 1988.

Otis R. Bowen,

Secretary.

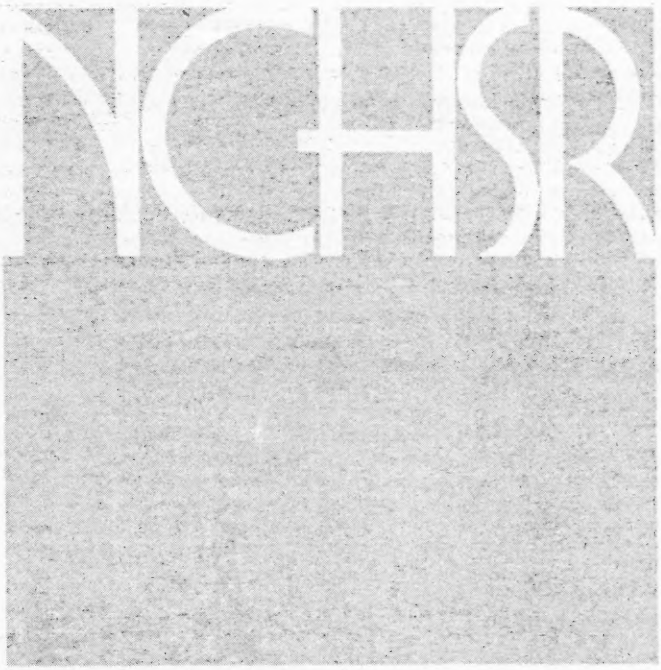
BILLING CODE 4120-01-M

APPENDIX I - Public Health Service Reassessment of Single Photon Absorptiometry for Measuring Bone Mineral Density - 1986

Health Technology Assessment Reports, 1986

Single Photon Absorptiometry for Measuring Bone Mineral Density

Number 7



NATIONAL CENTER FOR HEALTH SERVICES RESEARCH AND HEALTH CARE TECHNOLOGY ASSESSMENT

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service

FOREWORD

The Office of Health Technology Assessment (OHTA) evaluates the safety and effectiveness of new or unestablished medical technologies that are being considered for coverage under Medicare. These assessments are performed at the request of the Health Care Financing Administration (HCFA). They are the basis for recommendations to HCFA regarding coverage policy decisions under Medicare.

Questions about Medicare coverage for certain health care technologies are directed to HCFA by such interested parties as insurers, manufacturers, Medicare contractors and practitioners. Those questions of a medical, scientific, or technical nature are formally referred to OHTA for assessment.

OHTA's assessment process includes a comprehensive review of the medical literature and emphasizes broad and open participation from within and outside the Federal Government. A range of expert advice is obtained by widely publicizing the plans for conducting the assessment through publication of an announcement in the Federal Register and solicitation of input from Federal agencies, medical specialty societies, insurers, and manufacturers. The involvement of these experts helps assure inclusion of the experienced and varying viewpoints needed to round out the data derived from individual scientific studies in the medical literature. After OHTA receives information from experts and the scientific literature, the results are analyzed and synthesized into an assessment report. Each report represents a detailed analysis of the safety, clinical effectiveness, and uses of new or unestablished medical technologies considered for Medicare coverage. These Health Technology Assessment Reports form the basis for the Public Health Service recommendations to HCFA and are disseminated widely.

Individual reports are available to the public once HCFA has made a coverage decision regarding the subject technology. OHTA also publishes compilations which contain all assessment reports submitted to HCFA in a given calendar year.

OHTA is part of the National Center for Health Services Research and Health Care Technology Assessment, Public Health Service, Department of Health and Human Services.

Enrique D. Carter, M.D.
Director, Office of Health Technology Assessment

Samuel Lin, M.D., Ph.D.
Acting Director, National Center for Health Services Research and Health Care Technology Assessment

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PUBLIC HEALTH SERVICE REASSESSMENT SINGLE PHOTON ABSORPTIOMETRY FOR MEASURING BONE MINERAL DENSITY 1986

INTRODUCTION

Single photon absorptiometry (SPA) is a noninvasive radiologic technique used to assess bone mineral content in the appendicular skeleton (1). A photon beam from a sealed, single, low-energy radioisotope source is directed at a bone of the patient's limb, usually the shaft of the radius. As the beam passes through the bone and soft tissue, some photons are absorbed, and a nuclear counting instrument measures the intensity of the beam that emerges. The difference in photon absorption between bone and soft tissue allows for the calculation of the total bone mineral found in the scan path. The amount of skeletal mineral present is proportional to the change in beam intensity over the bone (2). The measurements by SPA are calibrated with known bone mineral content (BMC) from ashed bone sections or from standards calibrated against ashed bone sections. The SPA technique provides no information about the volume of bone scanned. In SPA, bone mineral is expressed in mass per unit length of bone (g/cm). Measurements of bone mineral by SPA have been used to provide an index of skeletal status in the assessment of a wide range of metabolic bone disorders such as renal osteodystrophy and osteoporosis.

First described in 1963, SPA is considered a simple, widely available, and relatively inexpensive bone mineral measurement technique (3). Initially, bones of the hands, humerus, femur, tibia, mandible, and calcaneus (os calcis or heel) were measured. Because of easy access to the forearm (radius) and better reproducibility, the

greatest experience has been collected with the forearm bones as scanning sites (1). Frequently used sites on the radius are the distal portion (10 percent of the total length from the styloid process of the ulna), distal third, and midradius. In current practice most radial bone measurements are limited to the midradius. For photon absorptiometry the midradius is a site two-thirds the length of the ulna from its proximal end. Some investigators also use measurements on ulna and radius together at the distal end of the radius (1). In the last 10 years, measurements of bone mineral in the forearms by SPA have become one of the most widely used methods for evaluating the cortical bone mass (4).

Recently, interest has centered on measurements of axial trabecular bone mass. Most nontraumatic fractures occur in the axial skeleton (spine) and proximal femur (hip), sites containing significant amounts of trabecular bone. Also, according to some investigators, bone mineral density (BMD) measurements made at the fracture sites (spine and hip) discriminate better between nontraumatic fragility fractures and nonfracture cases than measurements made on other parts of the skeleton (5,6). This has fueled a controversy regarding the value of radial appendicular (cortical) skeletal measurements for predicting the risk of developing a fracture at the spine or hip and monitoring the effects of therapy of osteoporosis. This recent interest in measurements of trabecular bone mass has also resulted in attempts to measure appendicular trabecular bone at the distal radius and os calcis. A major difficulty in measurements at these sites is the tapering bone and repositioning problem. Since the bone's cross section tapers sharply at the distal radius and is irregular at the os calcis, a small positioning change may produce a substantial change in bone diameter and measured BMD (5). According to Mazess, however, microcomputer-controlled instruments coupled to rectilinear scanners will greatly improve the precision of these instruments in sites where there is great variation in the bone cross section from one centimeter to another along the shaft of a

given bone (i.e., distal radius) (7). Rectilinear scanning of 1 cm segments of bone in 1 to 2 mm step-wise increments allows the averaging of multiple scans and improves precision.

SPA was first described by Cameron and Sorensen in 1963 (8). It was developed in an attempt to circumvent some of the problems inherent in the use of photodensitometry and radiogrammetry to measure BMD (8). The technique of SPA utilizes a well collimated beam of mono-energetic radiation, usually from I^{125} (200m Ci), to scan a peripheral bone (8). The absorption of photons is measured by a sodium iodide-thallium detector fixed on a C-frame opposite the photon source. This assembly synchronously scans across the bone being measured. Like radiogrammetry, SPA is limited to measurements of appendicular bone because tissue composition surrounding the bone has to be uniform and minimal. Corrections cannot be made by this instrument for bulk soft tissue or its uneven distribution around the bone. Because the technique requires a uniform soft tissue thickness surrounding the bone, the limb is immersed in water or wrapped with a water bag or tissue-equivalent material to simulate constant thickness in soft tissue (9).

Using SPA, the bone mineral measured reflects the total integrated mineral (cortical and trabecular) in the path of the beam. Calculations of bone mass in gm/cm are made with the use of standard curves. Standard curves are obtained by dividing an excised radius in pieces of 1-cm length and then scanning in the middle of these pieces. Scanning is performed under 4 cm of water. The 1-cm pieces are then ashed to constant weight. The calibration curve (standard curve) is obtained by plotting the ash weight of the dried, defatted human radius against the bone mineral as estimated with the SPA device (10). The units most frequently used with SPA are ash weight (in grams) per axial bone length (in centimeters).

SPA scans of the forearm take about 10 to 15 minutes and can be performed without specific preparation on most patients. According to Wahner, measurements of bone mineral with SPA are contraindicated in patients with skeletal abnormalities or history of fracture of the radius, recent immobilization of the arm, arthritic changes, or arteriovenous fistulas as used in renal dialysis (10). Costs for these devices range from about $19,000 to $25,000 (costs do not include radioactive source). The 200m Ci I^{125} radiation source that is required has a half life of 60 days. This source will have to be replaced every 4 to 5 months at a cost of about $750. Charges for the procedure range from about $50 to $150 (2). A comparison of SPA costs with those of other techniques for measuring bone mineral can be found in the costs section of the OHTA assessment for dual photon absorptiometry (DPA) (11).

Radiation exposure is always a concern with any procedure utilizing radiation sources. While SPA is a noninvasive technique, it does involve patient exposure to radiation. Wahner and colleagues have performed dosimetry measurements at the Mayo Clinic. They measured patient radiation dose from SPA of the radius utilizing I^{125} and four passes 1 mm apart. They found that the peak skin dose, with background measured at both eye and gonad sites, was 13 mrad (1).

According to the position paper on radiologic methods to evaluate BMC from the Health and Public Policy Committee of the American College of Physicians, SPA involves minimal radiation exposure, with negligible bone marrow or gonadal radiation (2). The position paper reports SPA involves a 2 to 5 mrad dose to the limb. The body dose is negligible as a result of little radiation scatter. Physicians are required to obtain the Nuclear Regulatory Commission Level VI license to handle the necessary 400 millicuries of I^{125} used in SPA (3).

The physiologic information provided by measurements of BMC have been under extensive investigation during the past 20 years. Bone mass measurements have been a valuable research tool for clinical investigations attempting to elucidate the

pathogenesis of metabolic bone diseases. Investigators have sought to determine the clinical significance of bone loss with aging and bone disease and its relationship to an increasing risk of fractures among the elderly. This growing interest in better understanding the nature and degree of changes in BMC with age, with osteoporosis, and with metabolic bone disease, in general, has prompted the development of noninvasive measurement techniques for assessing bone mineral content (12). A variety of such techniques in addition to SPA are presently available. They include: radiogrammetry, photodensitometry, radiographic absorptiometry, computed tomography, and DPA.

Although bone mineral measurements with SPA have been utilized mostly in studies of primary osteoporosis, a number of clinical investigations have been reported regarding its use in renal osteodystrophy (13,14,15,16,17). These studies which include work by Stewart and associates, Atkinson and colleagues and Griffiths and Zimmerman indicate that photon absorptiometry is suitable for epidemiological studies and clinical research in metabolic bone diseases associated with renal failure (13,14,17). However, the role of SPA measurements for individual case diagnosis and for patient management decisions is uncertain (6,14,16).

Many of the methods of bone mass quantitation in general, and SPA in particular, have been used in attempts to diagnose osteoporosis or to follow its response to therapy. This report will reassess the effectiveness of SPA bone mineral measurements on the clinical outcome of patients being evaluated and treated for osteopenic bone diseases. This reassessment seeks to ascertain where bone mineral evaluation by SPA fits into the overall scheme of osteoporosis prevention, diagnosis and treatment. A similar report has been published on DPA. The other noninvasive measurement techniques for bone mineral will be assessed subsequently, in separate reports.

BACKGROUND

Osteoporosis is a major public health problem. The National Institutes of Health Consensus Development Conference on Osteoporosis held on April 2-4, 1984, reported that osteoporosis may affect between 15 and 20 million Americans (18). More than 1 million fractures attributable to osteoporosis occur annually in individuals over the age of 45. Twenty-five percent of women over 60 years of age have documented vertebral fractures in association with osteoporosis. As many as 50 percent of women will develop vertebral fractures by age 75. These fractures may develop during routine activities, such as bending, lifting, or raising from a chair or bed (18). While compression fractures (collapsed fractures) of the vertebrae can produce severe pain, the amount of back pain and disability attributable to most vertebral fractures is unknown. According to the American College of Obstetricians and Gynecologists, after age 45 there is a marked increase in the incidence of distal forearm fractures (19). By age 60, there are 10 times more forearm fractures in women than in men of comparable age. These fractures limit the use of the extremity for 4 to 8 weeks, with long-term disability uncommon. While osteoporosis predisposes to fractures of various bones, hip fractures are the most serious in terms of disability, mortality and aggregate cost. In the United States, it is estimated that more than 200,000 hip fractures occur in elderly women each year with 80 percent found to be related to pre-existing osteoporosis (19). The affected population tends to be advanced in age and the sex distribution less skewed toward females than is the case with vertebral fractures. Acute complications such as depression and mechanical failure of the surgical procedure are common (18). Most patients fail to recover normal activity. Hip fractures lead to fatalities in 12 to 20 percent of cases and precipitate long-term nursing home care for half of those who survive (20,21). Hip fractures pose a significant economic as well as a medical burden.

The economic burden of all age-related fractures is great because of the large number of people involved and the expensive and protracted care that is often required. About a fourth of all patients with limb fractures require hospitalization and the mean hospital stay increases from 13.6 days among those age 25 to 44, to 32.6 days among those older than age 65. Fractures of the proximal femur account for more than half of all days of hospitalization for limb fractures. The cost of the acute care alone for fractures of the proximal femur has been estimated to exceed $1 billion annually in the United States (22). The direct and indirect costs of osteoporosis, including hip fractures, are estimated to be between $3.5 billion and $6.1 billion annually in the United States (18,21). As a result of the considerable morbidity, mortality and expenditures associated with this disease, there is growing interest in research regarding its prevention, diagnosis, and treatment. The pathogenesis of osteoporosis, its prevention and management has had extensive review. A summary of that information can be found in the osteoporosis section of the OHTA assessment on DPA (11). Additional information can also be obtained from the numerous references cited in that report.

For the past 5 years investigators have used SPA to assess the BMC of the appendicular skeleton in "normal" individuals and in patients with osteoporosis. Studies have been conducted to investigate whether appendicular (radial) bone mineral measurements could separate "normal" women from women with vertebral compression fractures or femoral neck fractures. Recently, some investigators have used SPA distal radial and os calcis measurements ostensibly to identify women at risk of future fractures. This report examines these and other studies as well as other evidence that pertains to the safety and clinical effectiveness of this technique.

RATIONALE

The rationale for bone mineral measurements in osteoporosis is based on the demonstration that the strength or resistance of a bone to fracture is closely related to the amount of bony tissue or the mass of the mineral present in the bone. Proponents argue that since the (breaking) tensile strength of bone mass is related to its mineral content, measurements of bone mineral should be a more accurate method of determining fracture risk. Proponents of SPA believe that the ability to assess the direction and degree of changes in bone mineral content in the os calcis, distal radial and midradial sites facilitates the diagnosis and management of metabolic bone diseases, such as osteoporosis. They argue that information on bone mineral loss is clinically important for the monitoring of age-related bone loss, for the diagnosis and monitoring of bone loss resulting from metabolic bone disease, for the assessment of drug effects on bone mineralization, and for the accurate assessment of fracture risk at the spine and femoral neck. Proponents also argue that these measurements could prove useful as clinical guides to therapy in assessing the therapeutic responses of patients with osteopenia.

REVIEW OF AVAILABLE INFORMATION

Accuracy and Precision

Accuracy defines the degree to which a measurement, or an estimate based on measurements, represents the true value of the attribute that is being measured. In this case it refers to how well the measurement reflects actual mineral content. It is expressed as a coefficient of variation (or error of estimate) of the difference between actual and measured. In the determination of osteopenia, accuracy in the measurement of bone mass by SPA is of great importance.

A number of complex technical factors affect absorptiometry accuracy determinations in vivo. These include beam hardening, photon beam size, scattered radiation and spatial variation of soft tissue composition (23). SPA minimizes the effects of scattered radiation and beam hardening that contribute to that inaccuracy. The narrow beam (less than 5mm diameter) eliminates problems of scattered radiation while use of nonenergetic radiation minimizes the effects of selective filtration of the beam as it passes through a limb (beam hardening) (23). According to Judy, the error introduced by hardening, scatter, and finite beam size can be reduced to less than 2 percent by calibrating the measurement system with an ash study (23).

Sorenson and Cameron, and Christiansen and coworkers have demonstrated that the mineral content of a bone as determined by SPA is independent of the position of the bone relative to top and bottom of the soft tissue and independent of the orientation of the bone in the soft tissue (24,25). It is also independent of a constant thickness of overlying tissue. However, the distribution of fat in the arm is such that its thickness, as seen by the scanning beam, is not uniform. Therefore, the accuracy of SPA is limited by the uncertainty and variation of soft tissue composition over and in the bone. The magnitude of this error has been estimated to be from 2 percent to as large as 30 percent (23). To minimize artifacts introduced by variation in soft tissue, the limb being studied is immersed in water or wrapped in a tissue-equivalent substance to simulate constant thickness.

The instrumental accuracy of SPA using I^{125} as the photon source was determined by Cameron and coworkers in 1968 (26). Excised bones were measured under water to simulate the soft tissue surrounding the limb and the mass of ashed sections was compared with the absorptiometric measurement. The authors reported accuracies of 4 to 7 percent for the SPA technique. With technical modifications (a rapid scanning automated system) made during the study, the authors demonstrated improved accuracies of 2 to 4 percent. More recently, Rustgi and colleagues found a 6.5 percent difference

when they compared measured BMC values obtained by SPA with absolute values obtained by the ashing method (27). In a 1983 review of noninvasive methods for quantitating appendicular bone mass, Johnston concluded that SPA provided an accurate assessment of the amount of mineral with an error of estimate of about 5 to 6 percent (9). Preliminary results from a study of bone mass in 50 postmenopausal osteoporotic women at the University of Washington was recently reported by Chestnut at the National Institutes of Health Consensus Development Conference on Osteoporosis (28). With SPA measurements of the radius/ulna, he reported obtaining an accuracy of 3 to 4 percent. Similar findings of accuracy (1-4 percent) have been reported in the position paper on radiologic methods to evaluate bone mineral content from the Health and Public Policy Committee of the American College of Physicians (2).

For monitoring changes in bone mass, SPA bone mineral measurements have to be sufficiently precise (reproducible) to provide a correct estimate of these changes. Precision is important if the goal is to detect small changes, such as the 1 to 2 percent per year loss of bone mass found in many postmenopausal women. The coefficient of variation (CV) expressed in percent describes the precision or reproducibility of a given measurement. A number of published studies have reported the precision of repeated SPA measurements to be between 2 and 4 percent (8,28,29).

Because accurate repositioning of the bone site for repeated measurements is the principal determinant of precision, a number of modifications to improve the repositioning error, including rectilinear scanning, have been introduced in different instruments. Using microcomputers, scans of multiple paths about 1 mm apart are feasible, giving an integrated bone mass over some distance (1). According to Mazess, rectilinear scanning can reduce the usual 2 to 4 percent error of linear scans to 1 to 2 percent (7). Similar results, under strictly controlled conditions, have been reported by

Wahner and coworkers (1). Johnston has found the precision of repeated SPA measurements quite good: 1 to 2 percent in the research laboratory, and 2 to 5 percent in the clinical setting (9).

Clinical Applications

One of the earliest studies of bone demineralization, using SPA measurements, was performed by Smith and associates on 169 white women older than 50 years of age at Indiana University School of Medicine in 1972 (29). They measured bone mineral at two radial sites in 56 women with and 113 women without fractured vertebrae. Although measurements of bone mineral in the radius were significantly less in the group with collapsed vertebrae, the authors reported considerable overlap in measurement values for the fracture and nonfracture groups (29). Because there appeared to be a greater loss of bone mineral from the radial site (one-tenth of the forearm length from the distal radius) containing higher percentages of trabecular bone, Smith suggested that scans of the distal radius may better reflect loss of mass in the vertebrae (29).

In a 1975 study, Smith with other associates reported results similar to the results of his earlier study (30). Using SPA measurements of the radius in a larger group of fractured (108 women with vertebral body decreased at least one-third in height) and nonfractured (161 women) caucasian women age 50 or older, he demonstrated that the nonfractured group had significantly higher bone mineral values. Again there were significant overlaps between bone mineral values for osteoporotic and for normal subjects. A short followup of 278 women for 470 subject-years showed that women with low SPA measurements may have a greater risk of diverse types of fractures. He found that the incidence of vertebral fractures was inversely proportional to the initial bone mineral measurements taken at the radius (30). Smith concluded, however, that factors other than low bone mineral, such as degree of trauma, quality of bone and activity, may be determinants of fracture as well (30).

In a related study of SPA measurements of rates of mineral loss with aging, Smith and colleagues determined that estimates of rates of loss over periods less than 2 years were too low in precision to be useful (31). According to Smith, if an individual loses bone mineral at an average rate of about 1 percent per year, the precision of the technique which would allow the detection of such a rate must approach 1 percent if the loss is to be determined in 1 year. If the precision is greater than this, several years' time will be needed before the loss can be detected (31).

Similar studies involving bone mineral measurements in osteoporosis were conducted at Brookhaven National Laboratory (32). Cohen and associates attempted to diagnose osteoporosis, based on SPA bone mineral measurements of the radius. Cohen found a large inherent variability in the bone mineral measurements of the radius similar to those reported by Smith (29). He also was unable to normalize the bone mineral measurements for the size, age, and sex of the individual (32). According to Cohen, these factors often make SPA bone mineral measurements of the radius unsatisfactory for evaluation of the extent of osteoporosis in an individual. However, he does believe that bone mineral measurements on the radius can be used to distinguish an osteoporotic population from an age- and sex-matched normal population.

In a continuation of the work by Cohen (32), Aloia and coworkers determined whether changes in bone mineral measured by SPA in the midradius (8-cm site), following therapy for osteoporosis, reflected changes in skeletal mass (total-body calcium) as measured by total-body neutron activation analysis (TBNAA) (33). Thirty-six osteoporotic patients who underwent several therapeutic regimens were studied on two occasions approximately 9 months apart by SPA and TBNAA. Aloia found no apparent relationship between the changes in bone mineral measured by SPA in the midradius with the changes in total-body calcium. Aloia concluded that changes in bone mineral at the midradius (8-cm site) could not be extrapolated to indicate changes in skeletal mass. However, he noted that it was possible that differential rates of remodeling occurred

with therapy in various skeletal sites and that an increment in BMC of the radius could be accompanied by a decrement in total skeletal mass (33). Although Aloia suggested that a better correlation between SPA measured changes in bone mineral with changes in total-body calcium might have been obtained at a radial site with more trabecular bone (3-cm site), this site was not utilized because of its increased error in measurement (33).

Studies by Khairi and coworkers and Wahner and associates, published in 1976 and 1977 respectively, used SPA and Singh's Trabecular Pattern Index (Singh index) to assess skeletal status and to compare the ability of the two methods to single out osteoporosis-prone subjects (34,35). Both groups reported that neither of the methods clearly separated the subjects with fracture from those without fracture. The study by Khairi prospectively followed 106 women, 70 to 95 years old, for 2 to 3 years after obtaining initial SPA bone mineral measurements and a Singh index (34). Noting that the total numbers of subjects and fractures (n=29) were few, Khairi reported that the incidence of subsequent fractures showed a significant inverse correlation with the initial SPA bone mineral measurements at the distal radial site (34).

The data published by Wahner again confirmed that SPA bone mineral measurements of osteoporotic patients fall within the lower ranges of average bone mineral of the relevant cohorts (35). In his study, and in contrast to the findings of Khairi, Wahner found that the Singh index gave a better separation of osteoporotic patients and age-matched normals than SPA measurements. According to Wahner, the Singh index, which is based entirely on changes in trabecular bone, probably discriminates better because osteoporotic patients have a greater proportion of loss of trabecular bone of the axial skeleton than of cortical bone of the appendicular skeleton (35).

In 1981 Riggs and coworkers at the Mayo Clinic demonstrated differences in trabecular and cortical bone diminution in elderly normal subjects and in patients with spinal osteoporosis (36). In a cross-sectional study, Riggs compared trabecular and cortical bone diminution with aging by measuring bone mineral concurrently at sites in

the axial and appendicular skeleton. Bone mineral of the radius (mid and distal) was measured by SPA while bone mineral of the vertebrae was determined by DPA. According to Riggs, although there was still considerable overlap, spinal bone mineral measurements with DPA were able to discriminate patients with osteoporosis from age- and sex-matched normal subjects better than SPA bone mineral measurements on the radius (36). Riggs suggested that cortical bone and trabecular bone function as separate compartments, which differ in respect to onset and rate of bone loss. He concluded that direct spinal measurements of bone mineral are greatly superior to appendicular measurements for evaluating the severity of spinal osteoporosis (36).

According to the work of Manicourt and associates, however, the amount of bone estimated by SPA measurements at the distal radius (3-cm site) closely correlates with the amount of bone estimated by physical determination of porosity index in the iliac crest trabecular bone (37). Bone biopsy and SPA measurements were performed concomitantly on 40 subjects: 31 normal and 9 patients with one or more compression fractures of the vertebrae. Because the physiochemical data (i.e., porosity index) correlated with the bone mineral values, Manicourt suggested that SPA measurements of a single peripheral bone (radius) are representative of changes in the axial skeleton in normal and osteoporotic subjects. He also indicated that distal scans of the radius better reflected the axial skeleton mass than proximal scans (37).

In 1983 Jensen and colleagues reported finding a relationship between SPA bone mineral measurements in the distal part of the forearm of 70-year-old women and the frequency of postmenopausal fractures (38). In the 258 women studied they identified 131 osteoporotic fractures, i.e., vertebral, hip, proximal humerus, and distal forearm in 77 of the women. The main observation of the author was that the frequency of osteoporotic fractures was more than three times higher in the 40 percent of women with

the lowest bone mineral values than in the 20 percent of women with the highest values. Jensen concluded that there is an increased frequency of osteoporotic fractures associated with decreased SPA bone mineral measurements in the forearm (38).

Recently, Gupta and coworkers reported using SPA measurements to establish the presence of and/or determine the severity of osteoporosis (39). In 13 of 17 patients with a history of vertebral compression fractures they found reduced bone mineral values at the radial shaft. However, 4 patients (24 percent) with compression fractures had normal bone mineral values and 24 patients without fractures had reduced bone mineral values at the radial shaft. Gupta concluded that SPA measurements of the raidal shaft may not accurately reflect the state of the axial skeleton. He suggested, despite repositioning error, considering SPA measurements of the distal end of the radius or direct measurements of the axial skeleton by DPA (39).

Similar findings and conclusions regarding the relationship between radius and spinal bone mineral measurements were also reported by Mazess and associates (6). In that study, reported in 1984, SPA bone mineral measurements of the distal third of the radius (site one-third of the forearm length proximal to the styloid process of the ulna) were compared with DPA total-body bone mineral measurements (TBBM) and spinal measurements in normal and osteoporotic subjects. Mazess found in normal males and females, a relatively small error (6-10 percent) in estimating the status of the total skeleton or the spine from SPA bone mineral measurements on the radius (6). However, in osteoporotics there was little relation between measurements at these sites. According to Mazess, in metabolic bone disease such as osteoporosis, a preferential alteration of trabecular bone makes measurements at appendicular sites (radius) inappropriate. He concluded that preferential spinal osteopenia probably explains the poor diagnosis of osteoporosis based on forearm measurements and confirms the need for a direct measurement of trabecular bone at the spine (6).

The regions of the radius examined in most of the previously discussed studies have been composed mainly of cortical bone. Reference to these regions as 10 percent, one-third, and 50 percent sites technically refer to the length along the ulna. According to Schlenker and von Seggen's distribution of BMC and percentage of trabecular bone along the radius, the percentage of trabecular bone at the 10 percent site is less than 25 percent and the percentage of trabecular bone at the one-third and 50 percent sites is less than 10 percent (40). These sites are mainly cortical bone whereas the site of interest, the vertebrae, is predominantly trabecular bone.

Therefore, more recently, groups have reported their experience using SPA to study the radius at a site where the percentage of trabecular bone is similar to that found in the lumbar spine. This region on the radius has been referred to as the "distal or ultradistal site," and is determined by a specific radius-ulna gap. Distal radial bone mineral studies with SPA at a 5mm site (radius-ulna gap) have been performed by various groups, under the direction of Talmage, at the University of North Carolina School of Medicine. In one of those studies, Aubrey and associates determined the reliability of SPA measurements at the 5 mm distal radius site. In a cross-sectional study of more than 700 normal white women they obtained measurements at the 5 mm site relative to age (41). According to Aubrey use of the 5mm distance between the ulna and radius for SPA positioning allows for reproducible measurements at a distal site. Nonetheless, he showed that mispositioning at the 5mm site could result in measurement errors of 1 to 3 percent (41). However, he demonstrated a trabecular bone composition of greater than 50 percent at the 5mm site.

From the large cross-sectional study of 700 normal women ranging in age from 18 to 98 years, Aubrey found that there was minimal bone loss in the radius before the age of 50 (41). This was followed by an accelerated phase of bone loss that persisted for the remainder of life. The bone mineral values at the midradius and distal radius were very similar. To determine if the distal radius measurements were indicative of conditions

existing in the spine, Aubrey compared the SPA distal radius measurements to DPA lumbar bone measurements in 140 normal subjects (41). Based on the small population tested, Aubrey concluded that in "normal" women the bone loss with age at the distal radius 5 mm site correlated closely with generalized bone mineral loss of the axial skeleton.

In a subsequent study, by the same group, Grubb measured radius and lumbar spine bone density in a small population of postmenopausal white female patients with nontraumatic fractures and their age-matched controls (42). An osteopenic group without fractures was also examined. He found that bone density values at all sites (midradius, and distal radius and spine) in the patient populations were statistically reduced from the bone density values in the control population. While the density of the midradius in two patient groups (mean age 62 years) showed a 12 percent decrease in density from the control values, the density of both the lumbar vertebrae and the distal radius had decreased 25 percent. From an analysis of his measurements in patients, Grubb found a statistically significant correlation coefficient of 0.51 between bone density of the distal radius (5 mm site) and that of the lumbar spine. He concluded that in patients as well as controls, the density of the distal radius correlates well with that of the lumbar vertebrae (42).

According to Grubb, 95 percent of all the patients with nontraumatic fractures of the spine and hip had a distal radius density value of 325 mg/cm^2 or less (42). Based on this finding, he suggested that patients without fractures but with distal radius density values below this "at risk" value (325 mg/cm^2) be considered for further evaluation. However, almost 30 percent of the women with "at risk" distal radius measurements had normal lumbar bone measurements.

In an accompanying cross-sectional study, Jacobson and coworkers used SPA bone density measurements at the distal radius site of 5 mm to determine the effects of exercise on normal postmenopausal bone loss (43). Bone density also was measured at the

midradius and first metatarsal with SPA and at the spine with DPA. By comparing the bone density of women college athletes with non-athletes and adult athletic women with non-athletic women, Jacobson found that women who exercise regularly and intensely have elevated bone mass both in compact and trabecular areas. According to Jacobson, bone measurement values in the radius and lumbar spine in the oldest athletic group (55-75 years of age) were in the same range as for younger athletic women. Jacobson concluded that while the data suggest that a regular and sustained exercise program is beneficial in building and maintaining bone mass in women, longitudinal studies have to be carried out before the beneficial effects of exercise on adult bone mass could be thoroughly established (43).

In a similar cross-sectional study using SPA to examine appendicular trabecular bone in normal women, Nilas and colleagues reported that on a group basis, the bone loss at the distal forearm scan site corresponds to the spinal bone loss (4). However, because the relationships between forearm and spinal bone masses are modest, Nilas concluded that in individuals, spinal bone mineral cannot be predicted from bone measurements taken at the forearm. To measure appendicular trabecular bone, Nilas located the 8 mm site (radius-ulna gap) and scanned distally with 4 additional scans 2 mm apart. By comparing bone measurements in this site in 19 postmenopausal and 53 premenopausal women with bone measurements scanned proximal of the 8 mm site (cortical bone), Nilas found that postmenopausal trabecular bone loss was approximately seven times greater than cortical loss within the first 5 to 6 postmenopausal years (4).

According to Nilas, the normal calibration procedure usually recommended by the manufacturers of a single measurement of the standard before each patient is examined is insufficient and results in a precision of 2 to 3 percent (4). To eliminate machine drift and achieve a long-term reproducibility of 1 to 1.5 percent, Nilas also calibrated the system once a week by measuring an aluminum standard nine times for 54 scans.

In their review of the Nilas study and other studies using SPA to measure bone mineral at distal and ultradistal sites on the radius (and ulna), Wahner and colleagues suggested that measurements made at these sites be interpreted with caution until further data are available (5). According to Wahner, although investigators determine and use the correlation coefficient between bone density of the ultradistal radius and that of the lumbar spine to show a relationship between the two, it is not the appropriate parameter for predicting lumbar spine density from ultradistal radius density in an individual. He believes that the appropriate parameter is the 95 percent confidence interval (5). Wahner showed that studies in which the correlation coefficient was statistically significant (0.56) between bone density of the ultradistal radius and that of the lumbar spine could also have 95 percent confidence intervals of $\pm$ 22 percent. Wahner found similar 95 percent confidence intervals are obtained when predicting lumbar spine density from age alone (5).

Mazess has also reviewed the studies using SPA for measurements of the distal radius (44). He is in agreement with Wahner that correlation coefficients between bone density of the ultradistal radius and that of the lumbar spine are not the appropriate parameters for predicting lumbar spine density from ultradistal radius density in an individual. According to Mazess it would be impossible to accurately predict spinal density from the distal radius when the correlation was only 0.52 (44). He also argues that the 5 mm site, measured by some investigators, while containing more than 35 percent trabecular bone is not 50 percent as indicated. According to Mazess, studies thus far have not shown that the distal radius site is a better discriminator of osteoporosis than the radius shaft or is equal to the spine (44).

Recently, at the Garvan Institute of Medical Research in Australia, Pocock and coworkers examined the correlation between distal (8 mm) forearm BMC determined by SPA, and lumbar vertebral and femoral neck BMD determined by DPA (45). Significant correlations (p less than 0.001) were found between the measurements on the forearm

and at the two axial sites in their study of 80 women, 50 postmenopausal, aged 20 to 76 years. However, despite the significant correlation between BMD in the spine and hip and BMC of the forearm, there was a large scatter of individual values about the regression line (large standard error of the regression). According to the authors the standard error of the regression (13 percent spine and 12 percent hip) was too large to allow reliable prediction of either site from the other in a particular individual (45).

Pocock took different forearm BMC's as detection points and determined the sensitivity and specificity of SPA for lumbar spine mineral density below 0.97g/cm^2 (a value associated with increased fracture risk) (45). For prediction of lumbar spine osteopenia with a sensitivity of 88 percent, Pocock determined that the false positive rate was 91 percent. In order to achieve a specificity of 82 percent, Pocock found the false negative rate was 65 percent. Similar predictions were obtained at the femoral neck. Pocock concluded that despite the relatively small study population, the data show that forearm densitometry (8 mm site) cannot be used to detect (screen) reduced BMD in the lumbar vertebrae or femoral neck in postmenopausal females (45).

In a longitudinal study of 1,098 randomly selected women ranging in age from 43 to 80 years, Wasnich and associates determined the risk of fracture associated with varying photon absorptiometry BMC measurements at four skeletal sites (46). BMC of the os calcis, distal radius, and proximal radius was measured by SPA in all 1,098 women. These women have now been followed for 4.5 years. Of these women, 456 have had (subsequent to fracture occurrence) both lumbar spine scans (DPA) and x-rays. Among the 1,098 women followed for 4.5 years there were a total of 26 incident fractures. These included eight rib fractures, six fractures at the wrist and only one at the hip (46).

Wasnich compared the nonspine fracture incidence rates by quintile of bone mineral content at the proximal radius, distal radius, os calcis, and lumbar spine (46). Using estimated odds ratios for varying levels of BMC, he investigated the dose-response

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relationship of BMC to the risk of fracture. Wasnich determined that the risk of fracture was significantly increased with diminishing quintiles of BMC at most skeletal sites. Moreover, when subjects in the lowest BMC quintile were compared to those in the highest quintile, the greatest risk difference was found for the os calcis.

Because subjects in the lowest quintile of os calcis BMC had a nonspine fracture risk 10 times greater than subjects in the highest BMC quintile, Wasnich concluded that the os calcis BMC measurement was the best predictor of nonspine fracture risk (46). This would include hip fractures, although only one fracture at that site was included in the study. He also suggested, based on prevalence data, that the os calcis BMC measurement was the best overall indicator of spine fracture risk. The most significant relationship of BMC to spine fracture prevalence was observed for the os calcis ($p=0.026$) and the lumbar spine ($p=0.041$). Although the study did not relate BMC at the os calcis to subsequent spinal fracture incidence, Wasnich concluded that measurement of os calcis BMC may be useful for routine risk evaluation of perimenopausal women (46).

In a related study, Wasnich included prospective spinal fracture incidence data in order to evaluate the predictive power of photon absorptiometric bone mineral measurements at various sites for fracture risk at "all" skeletal sites combined (47). He hoped to determine which single skeletal measurement was the best predictor of fracture risk, irrespective of fracture site. Also, the small number of spinal incident fractures recorded may have necessitated combining the spine and appendicular incident fractures.

The 294 women of this study, ranging in age from about 44 to 79 years, were a random subsample of the population described in the previous report (46). A total of 17 incident fractures were observed which included 8 at the spine and 1 at the hip. Wasnich observed the most significant relationships of BMC to fracture risk for the os calcis ($p=0.009$) and the spine ($p=0.011$). When subjects in the lowest BMC quintile were

compared with those in the highest, the greatest risk difference was found for the os calcis. Subjects in the lowest quintile of os calcis BMC had a combined (global) fracture risk six times greater than subjects in the highest BMC quintile.

Wasnich concluded, however, that because of the small number of incident fractures, these results must be viewed as preliminary. He suggested that measurements at the os calcis and lumbar spine may prove to be useful for assessment of global (total) fracture risk (47).

In a followup to the previous work at North Carolina, Talmage and coworkers used SPA and DPA to study age-related bone loss at several skeletal sites (48). Bone mineral density was measured at the midradius, distal radius and lumbar spine in 1,105 asymptomatic non-athletic and 124 athletic Caucasian women aged 18-98 years.

In the non-athletes, Talmage observed that the BMD of the two radial sites and the lumbar spine correlated positively (48). He also found that an age-related increase in rate of loss of BMD occurred at each of the three sites. The approximate age at which the increase in the rate of BMD loss occurred corresponded roughly to the time of menopause. In order to explain the increase in rate of loss of BMD at the spine, not seen in other reports (36), Talmage indicated that this may be due to differences in sample size and the age distribution of the populations studied (48).

In the smaller population of athletes, defined as those women who exercised regularly three times per week for 9 months of the year for at least 5 years, no increase in the rate of bone density loss could be demonstrated at the two radial sites (48). The number of lumbar spine measurements (DPA) in this group was too small for analysis. According to Talmage, while the absence of a significant change in rate of bone loss in athletes could have been due to the relatively small number of subjects, it also suggested that regular sustained exercise programs may delay or minimize the increased rate of loss of BMD which occurs in non-athletic women in the perimenopausal period (48).

In contrast to the findings of Talmage (48), Riggs again reported finding striking differences in the patterns of appendicular and axial bone loss, over life, in women (49). Based on a longitudinal study of only 139 normal women aged 20-88 years, he concluded that vertebral bone loss began well before menopause and continued into old age, with only a trend toward midlife acceleration. According to Riggs, substantial amounts of bone lost from the axial skeleton prior to menopause suggest prophylactic intervention well before the menopause (49).

Recently, Ott and coworkers found that in women with osteoporosis there were no correlations between SPA, DPA, and CT measurements of 1-year changes in bone mass (50). In addition to the possibility of different rates of bone changes at different sites of the skeleton, Ott suggested that the lack of correlation between the measurements may be related to the precision of the techniques and magnitude of the changes in bone in osteoporosis. She concluded that the techniques used were not sufficiently precise to measure the small amount of change in bone after only 1 year (50). Riggs and Melton believe that measurements every 6 months over 2 to 3 years may be required to estimate individual rates of bone loss (21).

According to Ruff and Hayes, changes in bone geometry and in material properties, such as ultimate compressive and tensile strength and energy absorbed prior to failure, may be the most critical features of the skeletal aging process (51). Failure to measure these characteristics may account for the relatively low efficiency of photon absorptiometry in identifying individuals who are at high risk for fracture. Moreover, they believe that standardizing BMC by bone width can produce misleading results in locational, sex, and age comparisons. In order to compare BMC in different individuals, some kind of standardization of skeletal size (bone volume) must be carried out (51). The most common size-standardization procedure has been to divide BMC by total bone width across the path of the scan (1). However, based on a 1984 study, Ruff and Hayes do not

believe that bone width is a good index of true bone volume and suggest that variations reported in bone mineral mass are almost entirely due to variation in bone volume, not variation in bone density or mineralization (51).

DISCUSSION

The measurement of bone mass is an important tool in the study of metabolic bone diseases, particularly osteoporosis. Current interest is centered on the recent advances in the SPA technique. This interest is a result of the recent applicability of the SPA technique to measure appendicular bone sites (distal radius, os calcis) with quantities of trabecular bone similar to that of the spine and hip. While SPA is capable of measuring bone mineral and has advanced our knowledge of bone disease in general, its role in the management of the individual patient is uncertain.

It would be advantageous to be able to prospectively identify those women who are at risk of developing osteoporotic fractures, in order to direct treatment to those at greatest risk. As a screening test for osteoporosis in perimenopausal women, this application of SPA bone mineral measurements is suggested to have potential utility. Once established as a screening tool it could be used in the strategy for treating afflicted individuals or preventing osteoporosis. Although the technology to noninvasively measure bone mineral with SPA is currently available, the ability of such measurements to identify those individuals who will subsequently fracture has not yet been shown. In a prospective study of 1,098 women with diverse types of nonvertebral fractures, Wasnich and coworkers found that subjects in the lowest quintile of bone density, as measured by SPA, had a tenfold greater risk of some type of fracture than women in the highest quintile (46). Measurements of the bone density of the os calcis appeared to be a stronger predictor of fractures than measurements at other sites. According to other investigators, this study included too few fractures of the hip (one) or wrist (six) to assess

the value of SPA for predicting these fractures (52). In a subsequent study by Wasnich, which included prospective vertebral fracture incidence data, the author recommended that the results of that study be viewed as preliminary because of the small number of incident fractures included in the study (47).

Presently, there has been no prospective study demonstrating that the noninvasive measurement of bone mass by SPA can identify patients who will suffer fractures. In their 1984 review of the various noninvasive methods for bone mineral measurements, Wahner and colleagues concluded that there was no optimal technique available for mass screening for early osteoporosis (1). The American College of Physicians' Health and Public Policy Committee recently reviewed various radiologic methods for measuring BMD, including SPA, but made no recommendation about the use of these tests in routine screening for osteoporosis (2). In order to predict individuals' fracture risk, it would be necessary to study large population cohorts of women from various age groups and relate their specific bone measurements to prospective fracture incidence data collected over a sufficient period of time. From fracture incidence data, the risk ratio would provide an estimate of risk. This type of study would enable investigators to determine whether it would be possible to predict the risk of fracture from the initial bone density measurements. A patient's bone mass measured before or at menopause may indicate whether she has low or high bone mass for her age. It will not necessarily indicate whether she will fall into the high-risk group 10 to 15 years later, when fractures begin. The contribution of bone mass at maturity versus subsequent rates of loss is still largely unknown. Moreover, there exists a controversy regarding the selection of a screening site. While many investigators consider BMD measurements of the actual fracture site (spine and hip) paramount, others argue that fracture risk prediction and screening can be accomplished by appendicular (trabecular) BMD measurements.

According to some reports it would be a useful screening tool (42,46). However, according to other reports it would be of little value because it could not reliably predict the risk of fracture in the spine or hip (21,45).

Initially, investigators used SPA bone mineral measurements in attempts to find a specific level of bone density that clearly distinguished patients with vertebral osteoporosis. Those studies, including the work of Smith and associates (30), Cohen and associates (32), Khairi and coworkers (34), and Wahner and associates (35), have been largely unsuccessful. According to Smith, factors other than low bone mineral, such as degree of trauma, quality of bone, and activity, may be determinants of fracture as well. An individual subject with low bone mineral has only one of the factors which increases the risk of fracture (30). Although Cohen found SPA bone mineral measurements of the radius unsatisfactory for evaluation of the extent of osteoporosis in an individual, he believes that bone mineral measurements on the radius can be used to distinguish an osteoporotic population from an age- and sex-matched normal population (32).

Other published reports also suggest that forearm SPA would not reliably assess the state of the spine or hip. Mazess and colleagues found in normal males and females, a relatively small error (about 10 percent) in estimating the status of the spine from SPA bone mineral measurements on the radius (6). However, in osteoporotics there was little relation between measurements at these sites. According to Mazess, 30 to 40 percent of patients at risk will be missed by SPA measurements, even if those measurements are taken on the distal radius or the os calcis (53). Mazess concluded that preferential spinal osteopenia probably explains the poor diagnosis of osteoporosis based on forearm measurements and confirms the need for a direct measurement of trabecular bone at the spine (6).

Recently, studies of SPA have attempted to determine the clinical usefulness of SPA measurements at appendicular sites (distal and ultradistal radius) containing amounts of trabecular bone similar to that found in the lumbar spine. Jacobson (43) and Talmage (48) at the University of North Carolina School of Medicine used SPA measurements at the distal radius (5 mm site) to show differences in bone mass and bone loss in groups of atheltic and non-athletic women. In an accompanying study, Grubb found a statistically significant correlation between bone density of the distal radius and that of the lumbar spine. He concluded that in patients as well as controls, the density of the distal radius correlates well with that of the lumbar vertebrae (42).

However, studies by Nilas (4), Wahner (5), Mazess (44), and Pocock (45), indicate that a significant correlation between measurements at two sites (distal radius and lumbar spine) does not necessarily mean that one measurement may accurately predict the other. Although Nilas found that bone loss at the distal forearm scan site corresponded to spinal bone loss, he concluded that in individuals, spinal bone mineral could not be predicted from bone measurements taken at the forearm (4). Wahner showed that in the Nilas study, in which the correlation coefficient between bone density of the ultradistal radius and that of the lumbar spine was statistically significant, scatter of the data could result in an error in measurement prediction of $\pm$ 22 percent (5). According to Wahner the appropriate parameter for predicting lumbar spine density from ultradistal radius density in an individual is the 95 percent confidence interval.

Pocock and coworkers also found a significant correlation between BMD in the spine and hip and BMC of the forearm (8 mm site). However, he also reported that there was a large scatter of individual values about the regression line (large standard error of the regression). According to Pocock, significantly correlated measurements with a large standard error of the regression (scatter) will preclude a reliable prediction of one site from the other in a particular individual (45).

Moreover, as a screening technique for reduced BMD in the lumbar spine, Pocock showed that a sensitivity of 90 percent with SPA could only be achieved by accepting a specificity of 9 percent (45). This meant a false positive rate of about 90 percent. Similarly, for prediction of femoral neck osteopenia at a SPA sensitivity of 92 percent, Pocock found that the false positive rate was 87 percent.

Another clinical application proposed for the SPA technique has been the use of SPA measurements to monitor the rates of bone loss and the effectiveness of treatment. This could apply to the treatment of individuals with established osteoporosis and also to those receiving preventive regimens. Because rates of bone loss are relatively small compared with the reproducibility of the measurement, current methods for measuring bone mass, including SPA, may not be sufficiently precise for clinical decisions in an individual (52,54). SPA is reported to have a precision of 1 to 5 percent and the average rate of appendicular bone loss in women is 1 percent per year in the decade after, and less before natural menopause (9,52). According to Cummings and Black, measurement of women's rate of bone loss based on two measurements of bone mass over a period of time leaves considerable uncertainty about her rate of loss. Even a bone loss of 3 percent measured by a technique with a 2 percent reproducibility (SPA) leaves considerable uncertainty about the actual rate of loss (the 90 percent confidence interval for that change in bone mass varies from a 1.7 percent gain to a 7.7 percent loss) (52). Unless multiple measurements are made, a woman must lose a substantial amount of bone during the time between measurements before a physician can conclude that she is losing bone more rapidly than normal (52). However, even these additional measurements have uncertain value for predicting future rates of bone loss or assessing risk for fractures and would substantially increase the expense. According to Ott, until such time as more sophisticated methods of improving the reproducibility are developed, techniques for measuring bone mineral, such as SPA, will be valuable in studying large groups of patients but will not be helpful in individuals (54).

With adequate precision, the high accuracy of SPA, together with its low radiation dose (2-5 mrad), would suggest that it would be particularly suitable for determining rates of bone loss by sequential measurements. However, for single measurements, there would be uncertainty as to whether the results would reliably reflect bone loss in the spine and hip.

Advice and comments concerning the safety and clinical effectiveness of SPA have been sought from groups and organizations within and outside of the Federal Government. An announcement of this assessment appeared in the Federal Register notice of October 26, 1984 (55). On June 20, 1985, in testimony before the Subcommittee on Aging of the Committee on Labor and Human Resources, United States Senate, the National Institutes of Health (NIH) through the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases (NIADDK) stated that it was a research imperative to develop methods for measuring bone density (56). In addition to diagnosis, these methods should enable early identification of bones most vulnerable to fracture and provide a measure by which to evaluate the effectiveness of new therapies. According to NIADDK, while several noninvasive methods for measuring bone density have been developed, at present no existing techniques can adequately discriminate early in the disease process between normal and osteoporotic individuals (56). The NIADDK recommended long-term clinical trials of various specific patient populations in numbers large enough to provide valid and reliable estimates of risk, and to determine the optimal regimens to prevent bone loss and fracture.

At that same hearing on osteoporosis, the National Institute on Aging (NIA) stated that there is a need for better ways of identifying persons at high risk of fracture, since those individuals could be expected to benefit most from treatment (20). Because it is still unclear which persons would benefit from which treatments and at what dosages and schedules, additional research and clinical trials are needed to develop the current state of knowledge regarding prevention and treatment of osteoporosis for specific individuals

or groups. The American College of Obstetricians and Gynecologists (ACOG), in their statement before the Subcommittee on Aging, indicated that presently, there are no tests to identify which women are at risk for developing osteoporosis (19). The College recommended, however, that the physician determine bone loss by absorptiometry in their diagnosis of osteoporosis.

Prior to the June 20, 1985, Senate Hearing on Osteoporosis, the National Institutes of Health (NIH) Consensus Development Conference on Osteoporosis was held on April 2-4, 1984 (18). At that conference, data were presented which showed that none of the noninvasive techniques for measuring bone mass were able to discriminate significantly between normal and osteoporotic individuals. None of the techniques for currently quantitating bone mass can definitely predict the individual at significant risk for osteoporosis prior to the occurrence of fracture. The Consensus Panel concluded that osteoporosis was a major public health problem requiring additional research on the biology of human bone, defining individuals at risk, and developing safe, effective, low-cost strategies for fracture prevention (18). The panel recommended studies to develop accurate, safe, inexpensive methods for determining the level of risk for osteoporosis in an individual, to establish early diagnosis, and to assess the clinical causes of the disease (18).

According to the Food and Drug Administration (FDA), SPA devices are pre-amendment products marketed prior to enactment of the Medical Device Amendments of May 28, 1976, to the Food, Drug, and Cosmetic Act. SPA devices are being marketed under Section 510(k) of the Medical Device Amendments to the Food, Drug, and Cosmetic Act. These devices have been proposed for classification as Class II devices.

Through its Clinical Efficacy Assessment Project, the American College of Physicians published a policy statement on radiologic methods to evaluate bone mineral content in June 1984 (2). The College concluded that all methods of BMC measurement result in significant overlap between diseased and normal populations. They stated that

the ultimate benefit of early diagnosis of metabolic bone disease will depend on the clear establishment of safe and effective treatments. The College believes that measurements of BMC have greater utility in following the course of a disease process or assessing the effect of therapy than in establishing a diagnosis. According to the College, none of the available techniques, including SPA, accurately predict tendency to fracture (2).

The Orthopedic Research Society strongly supports continued research in the development of noninvasive techniques for understanding metabolic bone disease. The Society suggested that the research examine the precision, accuracy, sensitivity, cost, availability, and relevance to underlying metabolic bone disease of each of the techniques currently under study. The Society also suggested holding a workshop directed at the understanding of the surveillance of bone disease.

It is the opinion of the Society of Nuclear Medicine that bone mineral density studies should become part of the work-up of patients with osteoporosis and that DPA is the technique of choice at this time. According to the Society, other methods performed on appendicular bone, such as SPA, are of little value in osteoporosis. However, they may have some application in renal bone disease.

A response from the American College of Nuclear Physicians stated that osteoporosis can be detected in its earliest stages by DPA measurements of the vertebral spine. According to the College, in order to postpone or prevent the problems of insidious progressive osteoporosis, early detection and screening by bone mineral analysis of the lumbar spine by DPA is critical. The College finds DPA of the spine far superior to SPA of the radius in detecting most cases of early osteoporosis. They suggest, however, that in older patients with significant degenerative spine disease, SPA measurements may be helpful in the management of an individual patient.

SUMMARY

SPA is a noninvasive radiologic technique used to assess BMC in the appendicular skeleton. A photon beam from a sealed, single, low-energy radioisotope source is directed at a bone of the patient's limb, usually the radius. The difference in photon absorption between bone and soft tissue allows for the calculation of the total bone mineral found in the scan path. With current equipment incorporating a rectilinear scanner and averaging multiple scans, the technique can achieve a precision of 1 to 2 percent with a radiation dose of 2 to 5 mrad.

The measurement of bone mass is an important tool in the study of metabolic bone diseases, particularly osteoporosis. While SPA is capable of measuring BMD and has advanced our knowledge of bone disease in general, its impact on the management of the individual patient is equivocal. Although the technology to measure bone mass noninvasively with SPA is currently available, the ability of such measurements at the os calcis and distal radius to predict individuals at risk of subsequently developing fractures of the spine and hip (screening) has not yet been shown.

Early studies with SPA that attempted to find a specific level of bone density that distinguished patients with vertebral osteoporosis from those without have been largely unsuccessful. Recently, studies with SPA measurements at the distal and ultra-distal radius have reported statistically significant correlations between bone density of the distal radius and that of the lumbar spine. However, a large scatter in the data precludes a reliable prediction of bone mineral from one site to another in a particular individual.

Other clinical applications proposed for the SPA technique have been the use of SPA measurements to monitor rates of bone loss and the effectiveness of treatment. A high degree of precision in the bone mass measurement is necessary for repeated

measurements of small degrees of change and such precision is difficult to attain. Presently, the suitability of the SPA technique for monitoring changes in bone loss is questionable.

Investigators have not distinguished between the use of SPA in clinical research and its role in day-to-day practice. SPA needs to undergo further clinical investigation before it can be recommended for general clinical use.

According to the FDA, SPA devices are pre-amendment products that were being marketed prior to enactment of the Medical Device Amendments of May 28, 1976, to the Food, Drug, and Cosmetic Act. SPA devices are allowed to be marketed pursuant to Section 510(k) of the Medical Device Amendments. Bone densitometers (SPA) have been proposed for classification as Class II devices.

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APPENDIX II - Public Health Service Assessment of Dual Photon Absorptiometry for Measuring Bone Mineral Density - 1986

Health Technology Assessment Reports, 1986

Dual Photon Absorptiometry for Measuring Bone Mineral Density

Number 6

NATIONAL CENTER FOR HEALTH SERVICES RESEARCH AND HEALTH CARE TECHNOLOGY ASSESSMENT

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service

FOREWORD

The Office of Health Technology Assessment (OHTA) evaluates the safety and effectiveness of new or unestablished medical technologies that are being considered for coverage under Medicare. These assessments are performed at the request of the Health Care Financing Administration (HCFA). They are the basis for recommendations to HCFA regarding coverage policy decisions under Medicare.

Questions about Medicare coverage for certain health care technologies are directed to HCFA by such interested parties as insurers, manufacturers, Medicare contractors and practitioners. Those questions of a medical, scientific, or technical nature are formally referred to OHTA for assessment.

OHTA's assessment process includes a comprehensive review of the medical literature and emphasizes broad and open participation from within and outside the Federal Government. A range of expert advice is obtained by widely publicizing the plans for conducting the assessment through publication of an announcement in the Federal Register and solicitation of input from Federal agencies, medical specialty societies, insurers, and manufacturers. The involvement of these experts helps assure inclusion of the experienced and varying viewpoints needed to round out the data derived from individual scientific studies in the medical literature. After OHTA receives information from experts and the scientific literature, the results are analyzed and synthesized into an assessment report. Each report represents a detailed analysis of the safety, clinical effectiveness, and uses of new or unestablished medical technologies considered for Medicare coverage. These Health Technology Assessment Reports form the basis for the Public Health Service recommendations to HCFA and are disseminated widely.

Individual reports are available to the public once HCFA has made a coverage decision regarding the subject technology. OHTA also publishes compilations which contain all assessment reports submitted to HCFA in a given calendar year.

OHTA is part of the National Center for Health Services Research and Health Care Technology Assessment, Public Health Service, Department of Health and Human Services.

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PUBLIC HEALTH SERVICE ASSESSMENT

DUAL PHOTON ABSORPTIOMETRY

FOR MEASURING BONE MINERAL DENSITY

1986

INTRODUCTION

Dual photon absorptiometry (DPA) is a noninvasive radiologic technique used to measure bone mineral density (BMD) in the lumbar spine (vertebrae) and proximal femur (hips). It can also be used to measure total skeletal calcium (1). The technique measures the transmission of a collimated beam of photons after they have been attenuated by bone and soft tissue. As the beam passes through the bone and soft tissue, some photons are absorbed, and a nuclear counting instrument measures the intensity of the beam that emerges. The difference in photon absorption between bone and soft tissue allows for the calculation of the total bone mineral found in the scan path (2). The amount of skeletal mineral present is proportional to change in beam intensity over the bone. The value of bone mineral given by DPA is determined by a calibration with known ash weights of lumbar vertebrae (in grams) L2-L4 or portions of the femoral neck or trochanter per area of bone scanned (in square centimeters). The DPA technique provides no information about the volume of bone scanned. Therefore, the term area result is expressed as mass of bone mineral per unit area scanned (g/cm^2) (3).

The physiologic information provided by measurements of bone mineral content (BMC) has been under extensive investigation during the past 20 years. Bone mass measurements have been a valuable research tool for clinical investigations attempting to elucidate the pathogenesis of metabolic bone diseases. Investigators have sought to determine the clinical significance of bone loss with aging and bone disease and its relationship to an increasing risk of fractures among the elderly. This growing interest in

better understanding the nature and degree of changes in BMC with age, with osteoporosis, and with metabolic bone disease in general has prompted the development of noninvasive measurement techniques for bone mineral density as a function of bone mineral content (4). A variety of such techniques are presently available. They include: radiogrammetry, photodensitometry, radiographic absorptiometry, single photon absorptiometry, computed tomography, and dual photon absorptiometry. These techniques for measuring bone mineral density are designed to assess bone mass. Their main application has been in diseases characterized by bone loss, which results from a number of defined disease processes, such as idiopathic osteoporosis, endocrine diseases, renal diseases, immobilization, and use of certain drugs such as corticosteroids and anticonvulsive drugs (5). Metabolic bone diseases, such as severe renal disease and hyperparathyroidism produce rapid bone loss. Changes of 20 to 30 percent in bone mineral content are possible in a short time. According to Wahner et al., these diseases rarely need quantification of bone loss by sophisticated techniques. For clinical patient management the evaluation of radiographs is generally sufficient (5).

Bone loss also occurs as a pathophysiologic process with aging. Although techniques of measuring bone mineral may assess the presence and degree of osteopenia, they give no information regarding the cause or mechanism of the loss. Many of these methods of bone mass quantitation in general and DPA in particular have been used in attempts to diagnose osteoporosis or to follow its response to therapy. The purpose of this report is to assess the safety and the effect of DPA bone mineral density measurements on the clinical outcome of these patients. This assessment seeks to ascertain where BMD evaluation by DPA fits into the overall scheme of bone disease prevention, diagnosis, and treatment. Other noninvasive measurement techniques for bone mineral will be assessed in separate reports.

BACKGROUND

Historical

In the 1960's standard radiographs were used in the early research attempts to measure BMD. One method, photodensitometry, was used to estimate bone mass by measuring the optical density of bone on x-ray films obtained under standardized conditions (6). The optical density of a radiographic image of bone is roughly proportional to the mineral mass of the exposed bone. The measurements on the film are made with a densitometer. Calibration of each film is accomplished by simultaneous exposure of a reference wedge. Photodensitometry, however, has technical problems relating to the radiographic technique (beam hardening, scattered radiation) and methods of film processing that limit its use (2). The photodensitometric method does not compensate adequately for factors such as soft-tissue thickness (7). Sensitivity to soft-tissue thickness restricts the application of photodensitometry to appendicular bones, particularly the phalanges.

Radiogrammetry (radiographic morphometry) is another method which uses standard radiographs to evaluate BMD. First introduced in 1960, this simple radiographic method measures the thickness of the cortex of metacarpal bones or other peripheral tubular bones (8). The most commonly used site is the second metacarpal of the nondominant hand, or several metacarpals from one or both hands (4). Based on the assumption that cortical thickness is a measure of mass, radiogrammetry uses the ratio of cortical to total width as a measure of bone density. Some investigators determine both cortical area and total area because they believe that cortical area correlates better with the amount of bone present than does cortical width. This method has been used extensively and a vast literature on its use is available on normal populations and on patient populations with various diseases. Radiogrammetry is well suited for detecting endosteal and periosteal cortical resorption with relatively good precision. However, no

evaluation of trabecular bone is possible using this method. Increased cortical porosity, which occurs in some diseases and with aging, is not detected. Radiogrammetry is not a good technique for estimating the quantity of trabecular bone in the spine.

An important breakthrough in the in vivo assessment of bone occurred in 1963, when Cameron and Sorenson introduced a low-energy radioisotope (I-125) photon absorptiometric method (9). Single-energy photon absorptiometry measures bone density in the appendicular skeleton. Measurements are usually obtained from the distal or midradius. This technique known as absorptiometry uses monoenergetic radiation passed across the bone, with the changes in beam intensity being recorded by a nuclear counting instrument (10). Like radiogrammetry, single photon absorptiometry (SPA) is applicable only to appendicular bones because tissue composition surrounding the bone has to be uniform and minimal. As in radiometric techniques (and in contrast to radiogrammetry), cortical and trabecular bone components are not separated, and the entire bone is measured at a cross-section (1). SPA has received extensive use in biomedical research on bone. In the late 1960's, investigators attempting to provide a means of measuring the peripheral skeleton without the necessity of embedding the limb in a layer of tissue-equivalent material, developed the method of DPA. With this new method, investigators also hoped to confront the significant clinical problem of fractures of the spine and proximal femur associated with osteoporosis. Believing that a direct measurement of bone mineral mass of the spine or hip would be clinically useful in addressing this problem, they sought to utilize the DPA method to measure the amount of bone mineral at these sites. With further development of DPA in the 1970's it became possible to measure bone mineral in the axial skeleton, particularly the lumbar spine and hips (11, 12). In the spine, the L2 to L4 region is usually measured because of the homogeneity of bone densities in these vertebrae and the absence of fractures (13). For the hip, bone mineral content is usually calculated from the femoral neck (cervical) and trochanteric regions.

Basic Principles of DPA

DPA is a modification of the single-energy technique using a radioisotope (Gd-153) that emits photons at two different energy levels. Dual photon absorptiometers reduce the effect of soft tissue on the absorption measurements in a two-component system consisting of soft-tissue and bone (13). Because of the different energy dependence of the gamma ray absorption coefficients in bone and soft tissue, dual-photon absorptiometers are capable of correcting for layers of fat and soft tissue overlying the bone. This permits the determination of the density of bone present, independent of the amount of soft tissue (11,14). This point will be addressed in greater detail in a subsequent section on precision and accuracy.

A typical dual photon bone mineral analyzer consists of a rectilinear scanner frame, a 1.0Curie (Ci) Gd-153 source, and a NaI (T1) scintillation detector (1). The system is interfaced with a computer that controls scanning pattern, speed, bone edge detection, data acquisition and other factors. To measure local areas of the axial skeleton, the radionuclide source is coupled to the collimated scintillation detector on a rigid yoke which moves in a rectilinear scanning mode across the spine or hips (1). The instruments are standardized with ashed bones or bone equivalent solutions in specially designed phantoms. Quality control phantoms are supplied and need to be used daily. In the measurement of bone mineral density the anatomic region of interest is scanned and a point-by-point determination of bone mineral is made. The transmission scan is obtained by counting the 42-keV and 100-keV gamma rays of Gd-153 after they have been attenuated by bone and soft tissue (12). The total bone mass is determined by summing the individual point values. The difference in photon absorption between bone and soft tissue allows for the calculation of the total BMC found in the scan path. BMC is inversely related to the measured transmission count rate (2). Using DPA, the bone

minera density measured reflects the total integrated mineral (cortical and trabecular) in the path of the beam. The BMD data, acquired during scanning, can be displayed either as a numerical print-out with a character plot or as an intensity modulated image (12).

Costs

DPA scans of the spine or femur take about 30 to 40 minutes and can be performed without specific preparation on any patient able to remain supine for that time. Several DPA instruments are available commercially. The capabilities of these instruments range from calculation of total skeletal calcium using BMD by DPA, to instruments for spine and hip, or spine alone. Costs for these devices range from about $30,000 to 40,000 for a spine scanner to about $65,000 for models capable of total body scanning (costs do not include radioactive source). The 1.0Ci Gd-153 radiation source that is required has a half-life of 242 days. This source will have to be replaced every 12-18 months at a cost of about $7,000 (15). As of June 1986, there were more than 300 facilities in the United States offering DPA. Charges for the procedure range from about $125 to $185 for a lumbar spine scan. If the femur scan is also performed an additional $60-90 is added to the cost (M. Duerst, written communication).

Among the alternative modalities SPA instruments cost $20,000 to $30,000. A typical SPA examination exposes the patient to 2 to 5 mrad of radiation and costs between $50 and $125 (2,16). The analysis software and calibration device (phantom) that are needed to do absorptiometry with a quantitative computed tomography scanner (QCT) can be purchased for $8,000 to $10,000 (17). A QCT examination typically takes less than one-half hour and costs average between $150 and $250, but can cost up to $400 in some settings (2,17). Low-dose QCT has been noted to expose the patient to a peak skin dose of as low as 300 mrad, but the dose can be as much as 500 to 1,000 mren (16).

OSTEOPOROSIS

Definition

Measurements of bone mineral density by DPA are being used extensively in epidemiologic, pathogenic, and therapeutic studies of osteoporosis. As a result of the considerable morbidity, mortality, and expenditures associated with this disease there is growing interest in research regarding its prevention, diagnosis and treatment. Osteoporosis is considered a major underlying cause of bone fractures in postmenopausal women and older persons in general. It (primary osteoporosis) is an age-related disorder characterized by decreased bone mass and by increased susceptibility to fractures in the absence of other recognizable causes of bone loss (18). Nordin believes that a bone is osteoporotic when the volume of tissue per unit volume of anatomic bone (volume/volume ratio) falls below the normal limit in young adults (19). According to Nordin if the value is within the normal range for the age and sex of the subject, "simple osteoporosis" is present. If the value is below the range for the age and sex of the subject, "accelerated osteoporosis" is present. Other investigators such as Riggs and colleagues use "postmenopausal" and "senile" classifications of osteoporosis (20). According to Riggs and colleagues, women with postmenopausal osteoporosis have lost excessive and disproportionate amounts of trabecular bone compared with peers. In contrast, bone loss in "senile osteoporosis" is proportionate for both cortical and trabecular bone and is only slightly more for patients with, than for those without, fracture (20).

Although osteoporosis affects all bones, fractures of the spine, wrist, and hip are most common. The risk of developing osteoporosis increases with age and is higher in women than in men, and in whites than in blacks (21). Two broad hypotheses have been proposed for the pathogenesis of primary osteoporosis. The first is that skeletal mass achieved at maturity is the critical determinant for development of clinical osteoporosis later in life (20). An underlying assumption of this theory is that the rate of bone loss is

not significantly increased in persons destined to become osteoporotic. This has been supported by the work of Hansson and Roos and Aloia and coworkers (22,23). Bone loss is considered a normal manifestation of the aging process. The second theory of pathogenesis is that those destined to become osteoporotic have significantly increased rates of bone loss by comparison with age- and sex-matched controls (24). The factors responsible for increased rates of bone loss in affected individuals may be the same as those operative during the aging process but are exaggerated. These two theories are not mutually exclusive, and presently it is not possible to state which one of these variables (bone mass at maturity or subsequent rate of loss) is more important.

Bone is composed of a collagen-rich organic matrix impregnated with minerals, largely calcium and phosphate. Two major forms of bone exist, cortical and trabecular. Cortical or compact bone forms the external envelopes of the skeleton. Trabecular or cancellous bone forms plates that traverse the internal cavities of the skeleton (25). The skeleton is 80 percent cortical bone and 20 percent trabecular bone. The proportions of cortical and trabecular bone vary at different sites. Vertebral bodies contain predominantly trabecular bone while the radius and proximal femur contain various contributions of cortical and trabecular components depending on the exact site analyzed (3). The responses of the two forms of bone to metabolic influences and their susceptibility to fracture appear to differ. Bone undergoes continuous remodeling throughout life in a constant, dynamic turnover consisting of bone formation and bone resorption. Peak bone mass is achieved at about 35 years of age for cortical bone and earlier for trabecular bone (18). Mazess reports that in women cortical bone mass shows a slow decline (3 percent per decade) until age 45 to 50 years and then an accelerated bone diminution (9 percent per decade) until age 75 (26). Similar findings have not been consistently obtained by other independent investigators or in men as compared with women. Cortical bone mass loss then decreases to about 3 to 4 percent per decade. In the same report, Mazess surveyed aging changes in trabecular bone and found that the

weight of evidence indicated decreases of trabecular bone beginning during young adulthood (20-40 years old) in both sexes and proceeding at similar rates (6 to 8 percent per decade) thereafter without evidence of age-dependent acceleration. This finding does not coincide with the assumption of an accelerated loss of trabecular bone after menopause.

Risk Factors

Bone mass is approximately 30 percent higher in men than in women, and approximately 10 percent higher in blacks than in whites. Peak adult bone mass in each person is suggested to be determined by a combination of genetic, mechanical, nutritional and hormonal factors (27). Other less well understood factors may also play a role. In each ethnic or gender group bone mass varies among individuals. After reaching its peak, bone mass declines throughout life because of an imbalance in bone turnover in favor of resorption over formation. The factors that appear to be responsible for age-related bone loss and predispose to osteoporotic fracture may include those that determine bone mass (27) and more. When bone mass is steadily lost the bones become fragile and more susceptible to fracture. As bones lose calcium and protein they may remain the same size but the walls of the cortical bone become thinner and the holes in the trabecular bone become larger (28). These changes in composition greatly weaken the structural integrity of the affected bone. While the exact pathogenesis of osteoporosis is not yet completely understood, low bone mass seems to be central to the disease process. Most of the known risk factors are causally related to the development of low bone mass. However, low bone mass is only one of the factors that is important in the pathogenesis of fracture. Trauma may also be important. Not all individuals with low bone mass will fracture. Some individuals will fracture despite relatively normal bone mass (29). Other diseases of the skeleton, e.g., osteomalacia, may occur with or without osteoporosis and may lead to osteopenia and an increased frequency of fractures. As mentioned above, the degree and frequency of trauma is also an important

determinant and some suggest that the frequency of falls increases as a function of age. Since muscle-wasting also occurs with age, the forces generated by a fall may not be widely distributed and may more easily result in fracture. According to Johnston, prevention of bone loss should lessen the frequency of fractures, but may not entirely eliminate the increased risk of fractures associated with aging (29).

Epidemiologic studies of patients who have fractures as well as studies of age-related bone loss, point to some of the factors that may predispose a person to develop osteoporosis. These studies suggest that the development and progression of primary osteoporosis may be enhanced by a variety of factors that upset the normal balance between bone formation and bone resorption. Some factors may be fortuitous associations commonly found among patients with osteoporosis. Risk factors, in addition to small peak adult bone mass, include estrogen deficiency (related either to aging or to premature menopause), other hormonal imbalances, low calcium intake for prolonged periods of time, or loss of calcium and vitamin deficiencies, or metabolic anomalies (most notably, involving vitamin D or hyperthyroidism) (30,31). Calcium deficiency may be an important risk factor because insufficient calcium intake during skeletal development may lead to a lower than expected skeletal mass at maturity. Calcium deficiency in the postmenopausal woman may lead to more rapid bone loss or less aggressive bone formation. While calcium deficiency is deleterious to bone mass, a number of studies found that calcium alone was ineffective against postmenopausal bone loss or less aggressive bone formation. Other risk factors include sedentary lifestyle (decreased mechanical loading) and alcohol or tobacco use or abuse (32,33). Dietary factors that may be involved in osteoporosis include high caffeine intake, high protein intake, and perhaps high phosphate intake (34). Bone mass and susceptibility to fracture may be at least, partly hereditary. No study has determined that family history of osteoporotic fracture is a risk factor for osteoporotic fractures. A small skeletal frame or leanness and northern European racial extraction also increase one's risk of developing

osteoporosis (35). For postmenopausal women, concurrent medical conditions or drug therapy affecting calcium balance (e.g., hyperthyroidism, corticosteroid therapy, or gastrectomy) are also considered clinical risk factors for osteoporosis. For elderly women, risk factors also include a history of previous fractures, a propensity to fall, and reduced mobility (29).

Prevalence and Incidence

Osteoporosis is a major public health problem. The National Institutes of Health Consensus Development Conference on Osteoporosis held on April 2-4, 1984, reported that osteoporosis may affect between 15 and 20 million Americans (36). More than one million fractures attributable to osteoporosis occur annually in individuals over the age of 45. Twenty-five percent of women over 60 years of age have documented vertebral fractures in association with osteoporosis. As many as 50 percent of women will develop vertebral fractures by age 75. These fractures may develop during routine activities such as bending, lifting, or raising from a chair or bed (36). According to the American College of Obstetricians and Gynecologists, after age 45 there is a marked increase in the incidence of distal forearm fractures (28). By age 60, there are ten times more forearm fractures in women than in men of comparable age. These fractures limit the use of the extremity for 4 to 8 weeks, with long-term disability uncommon. While osteoporosis predisposes to fractures of various bones, hip fractures are the most serious in terms of disability, mortality and aggregate cost. In the United States, it is estimated that more than 200,000 hip fractures occur in elderly women each year with 80 percent found to be related to pre-existing osteoporosis (28). The affected population tends to be advanced in age and the sex distribution less skewed toward females than is the case with vertebral fractures. Acute complications such as hospitalization, depression, and mechanical failure of the surgical procedure are common (36). Most patients fail to

recover normal activity. Hip fractures are fatal in 12 to 20 percent of cases, and precipitate long-term nursing home care for half of those who survive (37,38). Hip fractures pose a significant economic as well as a medical burden.

The economic burden of all age-related fractures is truly great because of the large number of people involved and the expensive and protracted care that is often required. About a fourth of all patients with limb fractures require hospitalization and the mean hospital stay increases from 13.6 days among those aged 25 to 44, to 32.6 days among those older than age 65. Fractures of the proximal femur account for more than half of all days of hospitalization for limb fractures. The cost of the acute care alone for fractures of the proximal femur has been estimated to exceed $1 billion annually in the United States (39). The direct and indirect costs of osteoporosis, including hip fractures, are estimated to be between $3.5 billion and $6.1 billion annually in the United States (36,38).

Treatment

The treatment of osteoporosis in postmenopausal women is considered both from the standpoint of preventive measures (prevention of further bone loss in normal women) and therapy of the patient with established disease and fractures (reversal of bone loss). At present, there is no reliable method to treat or reverse osteoporosis after it has been diagnosed (40). Nevertheless, investigators have recommended a variety of therapeutic regimens. The conservative approach in the management of patients with established osteoporosis and fractures has been the use of calcium with vitamin D supplements and an exercise program. According to Heaney there is a growing body of evidence suggesting that nutritional factors play important roles in age-related bone loss, particularly in the postmenopausal period in women (27). He adds that calcium is the most important of these factors and remains an important nutrient throughout adult life. With the aging population at risk of inadequate availability of calcium because of

low dietary intake and poor gastrointestinal absorption, Heaney recommended that postmenopausal women increase calcium intake to at least 1.5g per day if no estrogens were used. Similar recommendations have been made by Nordin and Johnston et al. (41,42). These recommendations are well above the estimated calcium intake of 500 mg per day in postmenopausal women in the United States and still above the recommended dietary allowance (RDA) of 800 mg per day. According to Nordin some 50 percent of women with clinical osteoporosis have malabsorption of calcium. Nordin treats these patients with small doses (0.25 ug per day) of calcitriol to increase calcium absorption (41).

Because postmenopausal osteoporosis is sometimes associated with low levels of plasma 1,25-dihydroxyvitamin D some investigators add therapeutic doses of vitamin D to the drug regimen (43). Avioli suggested that this approach was incorrect and recommended careful dietary and medical histories and measurements of plasma 1,25-dihydroxyvitamin D3 before vitamin D is added to the therapy. While Avioli reserves vitamin D therapy for patients with osteomalacia, he does recommend the use of diets or supplements, that contain at least 400 to 500 IU of vitamin D, to maintain nutritional adequacy (43). Riggs reported that the use of vitamin D was associated with a substantial incidence of hypercalcemia and hypercalciuria, or both. He also recommended that vitamin D not be included as a component of therapy (44). According to Audran recent reports have suggested that impaired formation of 1,25-dihydroxyvitamin D may play a role in senile osteoporosis (45).

According to Avioli, mobilization of the osteoporotic patient is an essential ingredient of any therapeutic protocol. He reported that moderate physical activity such as leg walk, sideward bends, arm crossing and chair pull in subjects aged 69 to 95 effectively retarded the rate of bone loss (43). Heaney believes that mechanical loading is probably the most important determinant of age-related bone loss and needs to be

maintained at as high a level as possible (27). However, not only does physical activity decline with age, but once the disease is present mechanical loading of the skeleton is even further decreased. Currently, it is not known how much mechanical stress is required, or how long it must be sustained to affect skeletal mass.

Although therapeutic intervention with calcium supplementation and moderate exercise programs represent the least risk to the patient, available evidence suggests, estrogen is more effective in preventing bone loss (32,46). Osteoporotic patients who are less than 10 years postmenopausal are usually offered estrogen replacement therapy (34,41,47,48). This therapy is usually combined with an adequate calcium intake of at least 1.0g of elemental calcium per day (41,47). Preliminary data by Ettinger et al. indicate that it may be possible to manage osteoporotic patients with a replacement dose of estrogen that is half as large (0.3 mg) as that presently recommended (0.625 mg) when the estrogen therapy is combined with high-dose calcium supplementation (1.5 g) (49). Nordin and colleagues reported estrogen therapy significantly reduced bone loss in women with crush fractures (50). According to Johnston and associates, calcium and/or estrogen therapy is probably of value in treating patients with crush fracture osteoporosis because of a slowing of the rate of subsequent bone loss and a reduction in the fracture rate (42). Currently, it has become popular to add progestins to the monthly estrogen regimen (48,25).

For symptomatic osteoporosis the therapeutic management of patients has also included fluorides, vitamin D metabolites, parathyroid hormone, diphosphonates, calcitonin, progestins, and anabolic steroids (34,51,52). These agents are used separately or in combination with calcium and/or estrogen. Some investigators question the value of therapies that only serve to prevent further loss of bone in patients already osteoporotic. They believe other measures are required to increase bone formation rate and improve bone density. Nordin suggests the use of anabolic steroids, Aloia, calcitonin whereas Riggs advises sodium fluoride and calcium therapy (41,51,44,). Only sodium

fluoride, in the presence of adequate calcium, has been shown to lead to increased bone mass and a decreased fracture rate (10,53). This regimen may require the addition of estrogen to achieve this goal. Unfortunately a large fraction of treated patients demonstrate serious side effects and many show little or no response to fluoride treatment. There is currently no way of predicting which patients will respond favorably to therapy (37). Additionally, data suggest that long-term use of fluoride leads to cortical bone loss in some patients which in turn may increase the risk of hip fractures. According to Riggs, several studies, including his own, have found that cortical bone decreases significantly during treatment (44). Perhaps the results of the two 5-year prospective double-blind randomized clinical trials supported by the National Institutes of Health will help determine whether problems with fluoride administration can be resolved.

According to Christiansen, there is no efficacious treatment of osteoporosis once symptoms have appeared (52). Lindsay states that treating established osteoporosis is difficult and emphasis should be placed on preventing further fractures rather than on increasing bone mass. He suggests removing environmental influences and treating health problems that may increase the risk of falls (34). After an extensive review of information regarding osteoporosis and osteoporotic fractures, Cummings and associates concluded, that in the already osteoporotic "elderly," prevention of falls seems to offer the greatest potential for reducing the risk of fractures (32). Because of the multifactorial etiology of osteoporosis many views of its causes, prevention, and treatment have been developed by the various specialties to whom these patients present.

Because there is no satisfactory treatment for established osteoporosis, prevention is especially important. To prevent osteoporosis in the immediate postmenopausal period many investigators recommend that patients alter controllable risk factors and increase

calcium intake. Exercise programs are also recommended. According to Heaney, the goal of prophylactic calcium supplementation and exercise is to achieve the highest possible peak bone mass before old age and to maintain that peak for as long as possible (27). Other researchers also believe that the pathologic effects of osteoporosis can be lessened and often eliminated simply by maintaining an "adequate" dietary intake of calcium throughout life and getting regular exercise (54,55). For preventive care in the young adult woman, Heaney recommends a high calcium intake, regular and vigorous exercise, and the avoidance of excess protein, alcohol, smoking and caffeine (27).

Currently, postmenopausal estrogen therapy appears to be the most effective single method for preventing bone loss and fractures in women (32,46). According to Johnston the strongest evidence available from published studies favors the effectiveness of estrogen, or estrogen/progestin combinations in preventing bone loss (42). Generally, investigators are reluctant to prophylactically treat with estrogens postmenopausal women who show no evidence of bone disease. Some recommend estrogen or estrogen/progestin prophylactic treatment for the high-risk group of women potentially liable to develop osteoporosis (31,52). Treatment is usually recommended to begin as soon as possible after the onset of menopause and to be continued for at least five years and perhaps as long as ten years or more (47). The National Institutes of Health Consensus Development Conference Panel concluded that estrogen replacement therapy and increased calcium intake are the mainstays of prevention and management of osteoporosis (36). The panel also indicated that exercise and nutrition may play an important role as well. It was noted, however, that until more data on risks and benefits are available, physicians and patients may prefer to reserve estrogen therapy for conditions that confer a high risk of developing osteoporosis, such as the occurrence of premature menopause.

In deciding whether estrogen should be administered, risks and benefits of estrogen therapy need to be considered. It has been reported that postmenopausal estrogen

therapy increases the risk of endometrial cancer (25,56). Most recently, the findings of Shapiro and associates suggest that long-term use of conjugated estrogen increases the risk of both localized and widespread endometrial cancer (57). The data also suggest that women who have taken conjugated estrogen for 1 or more years remain at increased risk for at least 10 years after they discontinue use. A similar finding of increased risk of endometrial cancer among users of conjugated estrogens has been reported by Buring and associates. This risk increases with longer use and higher dosages (56). According to Johnston and colleagues, the use of a progestin with the estrogen may reduce the risk of development of carcinoma of the uterus (42). In regard to breast cancer, Cummings and coworkers suggest that most evidence indicates the risk for breast cancer is not increased, although a few positive findings have been reported (32). The use of estrogen also entails the increased cost of medical followup and problems with patient compliance (44).

One potential benefit of estrogen, in addition to reducing bone loss, is the increasing evidence that estrogen therapy might protect against coronary heart disease in women (32). Studies assessing the risk of myocardial infarction and stroke in postmenopausal women taking predominantly unopposed estrogens are equivocal. More research is needed in this area. According to Haber, progestins which have been added to the monthly estrogen regimens to reduce the risk of endometrial cancer may also negate the beneficial effect of estrogen on coronary heart disease (48). In addition to a return of the menses a potential risk of progestin therapy is the increased risk of cardiovascular disease. Haber and other investigators recommend additional studies prior to the widespread and routine use of progestins (32,48).

In the past five years, investigators have used DPA to measure the BMD of the lumbar spine and proximal femur in "normal" individuals and in patients with osteoporosis. Studies have been conducted to investigate whether spine and/or hip bone mineral measurements could separate "normal" women from women with vertebral

compression fractures or femoral neck fractures. Recently, some investigators have used DPA measurements ostensibly to identify women at risk for future fractures. This report examines these and other studies as well as other available evidence that pertains to the safety and clinical effectiveness of this technique.

RATIONALE

The rationale for bone mineral measurements is based on the demonstration that the strength or resistance of a bone to fracture is closely related to the amount of bony tissue or the mass of the mineral present in the bone. Proponents argue that since the (breaking) tensile strength of bone is related to its mineral content, measurements of BMC at the actual sites of fracture should be the most accurate method of determining fracture risk. Proponents of DPA believe that the ability to determine accurately the direction and degree of changes in bone mineral density as a function of bone mineral content in the spine and proximal femur (sites of fracture) facilitates the diagnosis and management of metabolic bone diseases, such as osteoporosis. They argue that information on bone mineral loss is clinically important for the monitoring of age-related bone loss, for the diagnosis and monitoring of bone loss resulting from metabolic bone disease, for the assessment of drug effects on bone mineralization, and for the accurate assessment of fracture risk at specific bone sites (spine, femoral neck). Proponents also argue that these measurements could prove useful as clinical guides to therapy in assessing the therapeutic responses of patients with osteopenia.

REVIEW OF AVAILABLE INFORMATION

Accuracy and Precision

To determine the accuracy of DPA diagnostic tests, the measurement is compared with some independent measurement of bone mass, such as ash weight or physical density (58). Accuracy defines the degree to which a measurement, or an estimate based on measurements, represents the true value of the attribute that is being measured. In the determination of osteopenia, accuracy in the measurement of bone mass by DPA is of great importance.

A number of complex technical factors affect dual photon accuracy determinations in vivo. These necessitate corrections for deadtime of the counting system, beam hardening, and scattered radiation (59). When these corrections are made, measurements on bone phantoms (phantoms with known concentrations of dipotassium hydrogen phosphate solutions) have shown excellent accuracy. However, differences in laboratory practices can lead to variable results (7). The accuracy of DPA determined by Wilson and Madsen in bone phantoms was 1.2 percent (standard error of estimate) (11). Krolner and Pors Nielsen reported 1.3 percent (14). According to Mazess the accuracy error for DPA is 3 to 5 percent on actual vertebral or femoral specimens scanned under in vivo conditions (59). Genant reported 4 to 10 percent (60). Genant and associates believe that vertebral compressions, hypertrophy of articular facets, discogenic sclerosis or marginal osteophytosis and extra-osseous calcification, which are widespread in the elderly and are included in the integral measurements of DPA, may result in inaccurate as well as poorly reproducible vertebral measurements (61). Cohn reported that the accuracy of the DPA method (greater than 5 percent) is markedly reduced when the technique is used for measurement of the spinal column bone or any irregularly shaped bone surrounded by a large volume of tissue (62). He found systematic measurement

errors introduced by variation in the distribution of fat in the bone, and by the variable size and shape of the vertebrae, particularly after the vertebrae have been altered by a crush fracture.

Initial work by Wilson and Madsen (1977) and Krolner and Pors Nielsen (1980) showed that accurate results could be obtained regardless of soft tissue thickness or composition (11,14). It was shown that the influence of fat on the measured bone mineral would be negligible if the fat layer over the vertebrae had the same thickness as the fat layer over the site used for baseline measurements (14). However, a nonhomogeneous distribution of adipose tissue in the body areas transversed by the scanning radiation beam may lead to an underestimation or overestimation of BMC. Roos and associates, have found that fat in the adipose capsules of the kidneys may cause an overestimation of the bone mineral content in the third lumbar vertebra by DPA (63). Krolner and Pors Nielsen reported that a nonuniform increase in fat surrounding the lumbar spine may show a decrease of bone mineral density measurements (14). DPA attenuation equations assume that soft tissue is homogeneous, whereas in practice it consists of variable amounts of fat. Variations in fat-lean composition produce differences in the attenuation coefficients for soft tissue that influence measurements which may lead to erroneous results (14,64) According to Tothill, investigators have ignored the errors introduced by this factor (65). Mazess reported, however, that there is little influence of nonuniform tissue composition on bone, as might occur if composition above the spine differs from that surrounding it or if fat composition of the marrow varies (7). He reported that the variation in density measurements due to a 3 percent shift of fat is virtually undetectable. Recently, Wahner and colleagues have also reported on the effect of fat on DPA bone mineral density measurements (66). According to the investigators, bone mineral density measurements may be affected by changes in body

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fat, such as a nonuniform increase in fat surrounding the lumbar spine. Conversely, they found that changes in intraosseous and intramedullary fat had little effect on the measured bone mineral density (66).

Mazess found that a calcified aorta lying to the side of the spine can cause substantial problems in the soft tissue baseline determinations causing underestimation of bone mass. If the calcified aorta is above the spine the bone mass is overestimated (59). According to Mazess the use of an improper or average baseline can cause errors of 20 percent or more in bone determination. Because a soft tissue baseline can vary by 5 to 10 percent, Mazess recommends determining the soft tissue baseline along the entire length of the lumbar spine for accurate bone determinations (59). He identified the ribs, calcified aorta, transverse processes, and even the iliac crest as factors that could adversely affect baseline measurements. Mazess reported that incorporation of data from these locations into the soft tissue baseline measurement erroneously elevates the baseline and reduces the apparent BMC (59).

For monitoring changes in bone mass, DPA bone mineral measurements have to be sufficiently precise (reproducible) to provide an accurate estimate of these changes. The coefficient of variation, expressed in percent, describes how precise or repeatable a given measurement is. Several investigators have reported the in vivo precision of DPA to be better than 3 percent (coefficient of variation) (11,12,67). Krolner and Pors Nielsen found the coefficient of variation of repeated measurements ranges from 1.4 percent in normal premenopausal women to 2.6 percent in postmenopausal women with clinical osteoporosis (14). They suggest that the smallest significantly detectable difference in the women measured would be a BMD change of 4 percent in normal premenopausal women and 7.4 percent in postmenopausal women with clinical osteoporosis.

Because the clinical usefulness of bone mineral measurements depends on the long-term reproducibility of the applied method in vivo, Krolner and Pors Nielsen performed

long-term precision measurements of the BMD of the lumbar vertebrae utilizing DPA (68). In this study the BMD measurements were taken at 6- and 31-month intervals rather than the 14-day interval used in their earlier study. The authors concluded that the long-term reproducibility of DPA measurements in vivo must be based on measurements in vitro because of changes in lumbar BMC and fat distribution. From in vitro measurements they calculated a coefficient of variation of 1.4 to 2.5 percent in the BMD range of normal premenopausal women, and 2.0 to 7.9 percent in the BMD range of osteoporotic women with vertebral compression fractures (68). According to Mazess, the major problems for clinical use of DPA involve the precise and reproducible location of the measurement site (59). In the lumbar spine, poor spatial resolution and crush fractures can lead to uncertainties of positioning. To obtain maximum precision, LeBlanc and colleagues found that a previous scan must be compared directly with the current one (69). This was demonstrated by analyzing scans integrating a region intentionally shifted three lines above the originally chosen lines. Failure to compare the same area resulted in an additional error of 2 to 4 percent.

In this recent study, LeBlanc investigated the precision of two dual photon absorptiometers using scans of phantoms, normal subjects, and patients (69). He found phantom measurements for one instrument 2 to 5 percent lower than for the other. Moreover, the auto and manual methods of analysis gave significantly different BMD values for both instruments, with the manual method having better precision. According to LeBlanc, the manual/auto BMD differences result from a difference in edge selection. The automatic method used by the computer determined values for bone edges and baseline while the manual method involved a line-by-line inspection of edges and baseline. The author suggests that changes in analysis software might improve the automatic edge detection and therefore improve precision in this mode (69).

LeBlanc and colleagues determined that the average BMD percent precision error of the two instruments was 4 percent at a 95 percent confidence level (69). These

findings indicate that to be confident (95 percent) that a real change had occurred in BMC, two scans would have to differ by more than 5.6 percent. The authors also found, contrary to popular belief, that for observers with similar training interobserver analysis error was essentially equal to the intraobserver error.

Preliminary results from a study of bone mass in 50 postmenopausal osteoporotic women at the University of Washington was recently reported by Chesnut at the National Institutes of Health Consensus Development Conference on Osteoporosis (36). With DPA measurements of the spine, he reported obtaining a precision of 3 to 5 percent and an accuracy of 2 to 4 percent. Similar values for precision were obtained for DPA measurements of the femur. The accuracy of the femur measurements was not provided. These results were obtained with modifications made by the group at the University of Washington to the DPA scanner that resulted in scanning images that clearly delineated the vertebral bodies. According to Wahner and associates, part of the problem inherent in assessing the accuracy of DPA is associated with the determination of anatomic areas corresponding to the scanned areas (spatial resolution) on the highly variable vertebrae (70). Wahner and coworkers compared the BMD of 26 L2-L4 segments, removed from cadavers, and measured by DPA, with the area density determined from an ashed specimen of L3. They reported an error of about 5 to 6 percent in determining BMD in excised vertebrae with DPA. On the more uniform femoral neck they were able to obtain an accuracy of 3 to 4 percent with DPA (70).

Because relatively few longitudinal clinical studies have been performed to date utilizing DPA, little information is available regarding the effects of the Gd-153 source decay upon soft tissue correction. According to Pors Nielsen and Krolner the precision in vitro of the DPA method depends on the activity of the radioactive source (71). They found the coefficient of variation became two to three time higher when the radioactive source decayed from 1.2 to 0.4 Ci. Other problems regarding the radioactive source have

been reported. According to Wasnich and Vogel (written communication) the current algorithm for DPA does not correct appropriately for soft tissue effect as the Gd-153 source decays. However, this has not been reported by other investigators.

Bone Mass/Bone Strength

In osteoporosis, bone is decreased in amount, i.e., the bone mass is decreased per given volume. The bone cortex is thin. The trabeculae are decreased in number and size, increasing bone "porosity" and decreasing its tensile and compression strength (load-bearing capacity). Bone fracture represents the overriding clinical consequence of osteoporosis. When the skeleton is exposed to physiologic forces or to trauma, regions of it are subject to exceedingly great stresses. Fractures occur when the local stresses exceed the tensile and/or compressive strength of bone in that region (72). The relationship of bone strength and resistance to fracture to the quantity of bone (mass) had been studied in vitro by many investigators. In 1977 Martin and Atkinson reported on a study of 37 normal femoral specimens that determined the age- and sex-related changes in the structure and strength of the human femoral shaft (73). They observed that while the material strength of femoral bone decreases with aging for both sexes, the moment of inertia (second moments of area) of this structure increases for males but decreases for females. According to Martin and Atkinson, in males the increased moment of inertia compensates for the decline in material strength, whereas in females the diminution in both is additive and contributes to skeletal weakness (73). The investigators found that the male and female mean bone diameters did not reflect the differences in the moments of inertia observed between the sexes. Because the moment of inertia depends on the fourth power of the diameter only slight changes in the linear dimensions of the bone are needed to produce large differences in the moments of inertia

and structural strength. The authors observed a tendency for the endosteal or inside diameter in the female femoral sections to increase and the cortical thickness to decrease with age (73).

In a similar in vitro study, Wall and associates reported that both density and intrinsic strength of femoral bone increase up to about the fourth decade of life and then decrease with age (74). They noted that the rate of decrease of strength is greater than that of density. Strength decrease from the fourth to the eighth decade of life was about 20 percent, whereas the corresponding density decrease was only about 2.6 percent (74). According to Wall the data indicated that either strength is extremely sensitive to any change in the denisty of bone or other factors may play an important role in determining strength of bone. Some studies of the relation between compression strength of the vertebrae in relation to age suggest that strength increases with age until 30 years of age and thereafter decreases, with an appreciable drop after 50 (75).

When it became possible to determine in vivo the BMC as a function of BMD of separate vertebrae of the lumbar spine by DPA, studies were initiated to correlate BMD values and ultimate compressive strength of lumbar vertebrae. It was hoped that these measurements would provide a basis for estimations of normal and abnormal amounts of bone mineral in the vertebrae and to predict patient susceptibility to fracture. In 1980 Hansson and coworkers used DPA (Am-241/Cs-137) to measure the BMD of 109 lumbar vertebrae from 36 different autopsy subjects; mean age 59 years (76). After determination of the BMD, the ultimate compressive strength was determined by compression of the vertebral body until fracture occurred. The authors reported a statistically significant positive correlation between the BMD of all 109 lumbar vertebrae and the compressive load needed to cause a fracture ($R=0.86$, $P < 0.01$). Similar findings of mineral content that were highly correlated with resistance to compressive forces had been reported by Bell and colleagues for the vertebrae, and Dalen and associates in the femoral neck (77,78). Interestingly, in the study by Hansson the

posterior elements were not included when the vertebral bodies were compressed. According to the authors these parts of the vertebrae carry an almost negligible share of the axial load. However, the posterior elements and the vertebral bodies added almost equal proportions to the total BMD measured by DPA (76).

The findings of Hansson and colleagues suggested that BMD measurements of the lumbar vertebrae by DPA could be used as an indirect measure of ultimate compresssive strength (76). However, their findings of a linear correlation between the BMD (g/cm^2) of lumbar vertebrae and the ultimate compressive strength of their vertebral bodies is in disagreement with the findings of Bell and associates and Carter and Hayes (77,79). The findings of these investigators indicated that the compressive strength of bone is related to the square of the apparent density. Based on this relationship, which is similar to the findings of the earlier in vitro studies, small changes in apparent bone density can generate large changes in strength. Apparent density, expressed in g/cm^3, is the mass of bone tissue divided by the bulk volume of the test specimen, including mineralized bone and bone marrow spaces.

According to Ruff and Hayes, one structural variable that is not often considered in studies of skeletal aging of long bones is the global geometry of cortical bone (80). The investigators believe that the geometric distribution of bone tissue, together with its material properties, is critical in determining the structural strength and rigidity of the whole bone. To demonstrate this concept the investigators studied cortical bone remodeling with aging in femoral and tibial cross-sections obtained from an archeological collection (81). This Pecos Pueblo collection represents a large, late, prehistoric and protohistoric site in New Mexico. Ruff and Hayes observed increases with age in subperiosteal dimensions and second moments of area in both males and females. However, they also found that this remodeling process is modified by localized bone site differences in mechanical loadings, some of which are apparently sex-specific (81). According to Ruff and Hayes, regions, male or female, subjected to relatively high

mechanical stress in vivo would show the greatest increases with age in total subperiosteal area and second moments of area and the smallest decreases in compact cortical bone area. Conversely, regions with relatively less mechanical stimulation would show small increases (or actual decreases) in subperiosteal apposition of bone and second moments of area. Ruff and Hayes concluded that exercise-related apposition of bone on the subperiosteal surface may mechanically compensate for endosteal resorption and cortical thinning with aging, and reduce the risk of fracture among those individuals (male or female).

The authors believe that a difference in activity levels between their sample population and that of the Martin and Atkinson study could explain the difference in their findings (81). They suggest that the lifestyle of Pecos females subjected them to significantly more strenuous exercise than females from modern industrialized populations, the source of subjects for the Martin and Atkinson study. According to Ruff and Hayes these generally higher levels of activity could account for the greater apposition of bone throughout life among Pecos females (81). Chalmers and Ho cited greater physical activity as a contributing factor to the lower rate of hip fractures among the elderly, particularly women, in nonindustrialized as compared to Western industrialized populations (82).

The relative contribution of trabecular bone and the cortial shell to the load-bearing capacity of the vertebra has been the subject of much controversy. Because DPA provides an integrated measure of both cortical (30-40 percent) and trabecular contributions to mineral content, the contribution of the cortical shell to the load-bearing capacity of the vertebra is of extreme importance to the significance of the DPA measurements. This is especially true in light of the recent findings of Hayes and Gerhart that the cortical shell contributes very little to the overall strength of the vertebral body (72). Their work supports the earlier findings of Bell that the compression strength of the vertebrae depends almost entirely on the trabeculae, which form a three-

dimensional grid within the body (77). These findings, however, were not consistent with the observations of Rockoff and colleagues who reported that the cortical shell contributed 45-75 percent of the peak strength (83).

Clinical Applications

Spine. Investigators after initiating clinical studies established the feasibility of the DPA technique to measure bone mass at the spine and proximal femur. At the Mayo Clinic Riggs and associates studied the effectiveness of DPA to differentiate patients with idiopathic spinal osteoporosis (presence of nontraumatic compression fractures) from normal subjects (3). In that cross-sectional study reported in 1981, DPA was tested in a population of 105 normal women and 76 women patients with osteoporosis. Bone diminution with aging was assessed by measuring BMD concurrently at sites in the axial and the appendicular skeleton. BMC of the spine was assessed from scans of the L1 to L4 region. The BMD value included vertebral bodies and disk interspaces.

In normal women the authors found that vertebral bone loss began in young adulthood and continued linearly throughout life. In contrast to the findings in the appendicular skeleton there was no demonstration of an accelerated bone loss due to the menopause. The cumulative diminution of BMD from the vertebrae throughout life was 47 percent. Riggs and coworkers found that patients with osteoporosis had significantly lower mean BMD values at the vertebrae (p less than 0.001) compared with age comparable normal subjects. However, although the spinal measurements gave the best discrimination of osteoporotic patients from normal subjects there was still considerable overlap between the two groups (3).

To define spinal osteoporosis in terms of vertebral BMD rather than the presence of nontraumatic vertebral fractures the authors arbitrarily chose the 90th percentile for vertebral BMD for patients with nontraumatic vertebral fractures. This value, 0.965 g/cm^2 was then defined as the threshold below which the risk for nontraumatic vertebral

fractures increases. However, with this approach, by age 65 years, half of the women, and by age 85 years, virtually all of the women in the normal female population have BMD values below the threshold for fracture. All these women would be considered to have asymptomatic osteoporosis by the authors (3).

According to Riggs, the results of the study indicated that women with and without spinal osteoporosis lose substantial but similar amounts of cortical bone, but those with spinal osteoporosis lose more trabecular bone. The authors suggested that cortical bone and trabecular bone function as separate compartments which differ in respect to onset and rate of bone loss and possibly also in respect to homeostatic regulation. They believe that direct spinal measurements of bone density are greatly superior to appendicular measurements for evaluating the severity of spinal osteoporosis (3). However, because the lack of response of vertebral bone loss to menopause with DPA measurements was not consistent with the results of other studies, Riggs recommended that the effect of the menopause on the rate of bone loss in the vertebrae relative to that in the appendicular skeleton be studied further. Meunier and colleagues in a histological study of trabecular bone mass in iliac biopsy specimens from 236 control subjects found an acceleration of the linear diminution of trabecular bone as age increased in the postmenopausal period (84). Genant and associates reported a similar acceleration in bone loss at menopause in their study of vertebral mineral determination by quantitative computed tomography (85). According to the authors, the rate of integral spinal bone loss assessed by QCT is roughly one-half that of purely cancellous bone and may explain the difference in sensitivity with DPA. However, Krolner and Pors Nielsen assessed vertebral bone loss by DPA in a longitudinal study of 59 normal women and found an accelerated bone loss of nearly 6 percent immediately after the menopause (86).

Mazess proposed that the common assumption about a large ongoing loss of trabecular bone after menopause may be erroneous (26). He does not believe that the bases for assuming a disproportionate effect of estrogen on trabecular bone is well

supported. For example, he suggests that the apparent rapid loss of trabecular bone observed in the spine with quantitative computed tomography may be an overestimate due to the influence of an increasing fat content (26). According to Mazess, fractures of the vertebra and distal radius, which occur earliest in postmenopausal women, may be due to a trabecular bone loss that has a much earlier onset than that of compact bone loss and not to a more rapid rate of loss of trabecular bone. In contradistinction, the results of the recent study by Richelson and associates (1984) indicated that estrogen deficiency was the predominant cause of bone loss occurring during the first two decades after natural menopause (87). In that study DPA was used to determine the BMD at the femoral neck, femoral intertrochanter, and lumbar spine in 14 women who had undergone oophorectomy during young adulthood, in 14 normal perimenopausal women, and in 14 normal postmenopausal women.

Similar results were reported in an earlier study by Lindquist and associates (1981) on the influence of aging and menopause on BMC based on BMD measurements (88). In that cross-sectional study, bone density was determined in the third lumbar vertebra in a random sample of women by the DPA technique. The authors chose the ages of postmenopausal times in such a way as to make it possible to compare women of different ages but of similar menstrual status and women of different menstrual status but of similar age. According to the authors the results of the study support the hypothesis that there is an association between early menopause and accelerated bone loss (88). A 5-year longitudinal followup study by Lindquist and associates has confirmed the results of their previous cross-sectional study (89). When the same women had lumbar spine BMD determinations with DPA 5 years later the authors found larger differences in BMC between women of different menstrual status than between women of different ages. As in the cross-sectional study, the results from the longitudinal

followup indicated that the time of the menopause influences bone density, with significantly (p less than 0.01) lower values in those women who have an early menopause (89).

In a more recent longitudinal densitometric study, Riggs and coworkers found that vertebral loss in 139 normal women began well before menopause (90). Riggs measuring BMD at the lunbar spine for up to 3 years by DPA found continuous bone loss over adult life with a mean rate of loss of 1.2 percent per year. Moreover, rates of loss were similar in premenopausal and postmenopausal women. From this new data, Riggs concluded that the experimental design of the Richelson study, discussed above, was inadequate because the perimenopausal control group had already undergone substantial bone loss before menopause (90). He also suggested that oophorectomy might induce greater bone loss in young women in whom bone turnover is more active than in older women.

According to Riggs and coworkers there is a striking difference in the patterns of appendicular and axial bone loss in women throughout life (90). They confirmed only a small amount of cortical bone loss in the appendicular skeleton before menopause, with large amounts lost thereafter. By contrast, their longitudinal studies show vertebral bone loss begins well before menopause and continues linearly into old age with only a trend toward midlife acceleration.

Aloia and coworkers recently used DPA measurements of the spine in healthy women and women with vertebral crush fracture syndrome in their cross-sectional study of involutional bone loss (23). In contrast to the findings by Riggs and colleagues, Aloia determined that the best fit for the rate of involutional bone loss from the spine based on cross-sectional data was a two component curve. This indicated an accelerated loss of bone from the spine after menopause. Based on the available information, including published prospective data, Aloia concluded that there is an accelerated loss of bone from the spine after menopause (23).

In addition to the DPA measurements of the lumbar spine, the study by Aloia also included measurements of bone mass of the total skeleton and distal radius by in vivo neutron activation analysis, and SPA, respectively (23). The author found that the spinal measurements did not separate patients with osteoporosis from controls any better than the other bone mineral measurements. According to Aloia, although spinal bone mineral measurements could correctly classify about 77 percent of the cases, the number of misclassifications in the older age group of the normal women was substantial. Moreover, the bone mass measurements of the total skeleton, distal radius and spine determined by Aloia do not support the hypothesis of Riggs and colleagues (38) that women with vertebral crush fractures have preferential loss of spinal bone (23). According to Krolner the lumbar BMD of patients with only one vertebral fracture is less than 1.0 standard deviation (SD) below the age-matched normal mean (91). He suggests that women having their first spinal wedge fracture are indistinguishable from their normal peers as to the total bone mass of the lumbar vertebrae. Accelerated osteopenia of women having multiple vertebral fractures might be a consequence (immobilization) rather than a cause of fractures (91).

Other investigators have also used the DPA technique to measure the BMD of the spine and hip in populations of normal women and women with clinical osteoporosis. The technique was used by Schaadt and Bohr when they studied changes in BMD in the lumbar spine, femoral neck and femoral shaft in normal aging women, prednisone treated women, and in women with primary osteoporosis (92). Acccording to the authors the mean lumbar BMC measured by BMD of 19 women with primary osteoporosis was 31 percent lower than that of 36 postmenopausal age-matched controls. Bone mineral diminution in the femoral neck, which consists of a mixture of trabecular and cortical bone, was smaller than that of the lumbar spine but greater than that of the middle of the femoral shaft which consists of predominantly cortical bone. Schaadt and Bohr observed the same patterns of bone mineral loss in normal aging women and prednisone-

treated women. According to Schaadt and Bohr, the study demonstrated that in postmenopausal women and in the development of osteopenia, the loss of trabecular bone mineral is much greater than cortical bone loss. They suggested that direct measurement of BMC in the lumbar spine was necessary for an accurate evaluation of bone mineral status in that clinically important region (92).

In the Danish study by Krolner and Pors Nielsen, referred to earlier, the authors used DPA measurements of the spine in an attempt to differentiate women with spontaneous vertebral compression fractures or femoral neck fractures from normal women (86). The bone mass measurements were also to be used to identify women at risk of future fractures. BMD of the second, third, and fourth lumbar vertebrae was determined in normal women and women with clinical osteoporosis by using DPA in cross-sectional and longitudinal studies. According to Krolner and Pors Nielsen, the mean lumbar BMC of 86 women (aged 58-89 years) with primary osteoporosis was 41 percent lower than that of normal premenopausal women and 18 percent lower than that of age-matched controls. Nevertheless, the data showed, as did the data of Riggs (3), a large overlap between patients with clinical spinal osteoporosis and age-matched normals (86). The overlap is so large that the majority of patients with clinical spinal osteoporosis are indistinguishable from age-matched normals. Mazess reported that a very large overlap in the spinal density of fracture and nonfracture cases can be expected (93). Recently, he reported that about 60 percent of fractured lumbar vertebrae are entirely normal in density (94).

Krolner and Pors Nielson suggested that a difference in the duration (approximately 3 years) of accelerated bone loss in a subgroup of postmenopausal women in the early menopause could explain the 18 percent difference in lumbar BMC between patients and age-matched normals reported in their study. Krolner and Pors Nielsen point out that while the occurrence of vertebral compression fractures is related to bone mass, the significance of this quantitative approach <u>in vivo</u> remains uncertain. For example, a

minor loss of transverse trabeculae within the vertebrae that is barely detectable with the DPA method could contribute considerably to the weakening of the bone. The authors noted that arteriosclerosis of the lumbar aorta may account for nearly 15 percent of the measured BMD in severe osteopenia and give erroneously high values (86). In contrast, as noted by Cummings, the inclusion by Krolner and Pors Nielsen of subjects with nontoxic goiters, who might be on high doses of thyroid hormone, in the control population could result in erroneously low spinal bone density measurements for the control group (95).

In 1982, Krolner and associates reported on an investigation in a consecutive series of 132 women with and without osteopenia in whom radiography and DPA were compared (96). The investigators hoped to determine if a correlation existed between the two methods and if the loss of vertebral bone mass is concealed by the addition of bone mineral in nonrelevant structures such as the vertebral processes, osteophytes, and calcifications of the abdominal aorta. According to Krolner, the radiographic grade of osteopenia and the BMD of the lumbar vertebrae showed a significant inverse correlation. Each grade of radiographic osteopenia was associated with a large scatter in lumbar BMD. The overlap between normals and patients with obvious osteoporosis comprised nearly 60 percent of the cases with compression fractures. The data also suggested a considerable overestimation of the true vertebral bone mass when DPA was used in patients with osteophytes and severe aortic calcification. The authors found that spondylosis (osteophyte formation) accounted for 10 to 35 percent of the lumbar BMD measured in women with radiographically proven osteopenia. In severe osteopenia aortic calcification may account for nearly 10 percent of lumbar BMD (96).

Seeman and associates compared DPA BMD values of the lumbar spine to SPA BMD values for the radius in 100 patients with various types of endocrine dysfunction (97). The authors found that BMD in each endocrine disorder deviated in at least one site from the sex-specific age regression of 187 normal subjects. BMD measurements indicated

bone loss for patients with primary hyperparathyroidism, hypercortisolism, and hyperthyroidism. For patients with secondary hyperparathyroidism due to chronic renal failure, acromegaly, and postsurgical hypoparathyroidism the BMD measurements suggested bone gain. With the use of multivariate analyses of variance the authors found significant differences in the BMD measurements among the scanning sites. Seeman concluded that bone density of the appendicular and axial skeleton changes differentially in response to endocrine dysfunction and these changes are both site and disease specific. According to the authors, BMD measurements in the appendicular skeleton do not reliably predict BMD measurements of the lumbar spine. BMD changes induced by an endocrine or metabolic disorder mandate assessment of both the appendicular and the axial skeleton (97) Ott and coworkers have also suggested that in postmenopausal osteoporosis the bone may display different rates of change at different sites (98). Because the rate of change may be influenced by the relative amount of trabecular bone, the axial skeleton may not change at the same rate as the appendicular skeleton.

Ott studied longitudinal changes in bone mass after 1 year by DPA and other noninvasive measurement techniques in patients with osteoporosis (98). She found that in these women there were no correlations between measurements of 1-year changes in bone mass by the various techniques. In addition to the possibility of different rates of bone changes at different sites of the skeleton, Ott suggests that the lack of correlation between the measurements may be related to the precision of the techniques and the magnitude of the changes in bone in osteoporosis. She concluded that the techniques used (DPA, CT, SPA) were not sufficiently precise to measure the small amount of change in bone after only 1 year (98). Similar findings for DPA have been reported by Cohn, Krolner, and Cummings and Black (62,91,99). According to Riggs and Melton DPA measurements every 6 months over 2 to 3 years are required to estimate individual rates of bone loss (90).

Ott found that the precision of the DPA and CT techniques was lower in her

clinical setting than in some reports from the literature (98). Several factors probably contribute to this discrepancy. According to Cummings and Black scans obtained in carefully controlled research environments might have better reproducibility than scans obtained in other clinical settings (99). Also, claims of greatest precision are often based on repeated measurements of phantoms or bone specimens, or measurements in persons that are repeated within a short time. Persons cannot be repositioned or kept in position as well as phantoms or specimens (99). The study by Ott indicates that when these techniques for measuring bone mineral, including DPA, are applied to persons (more so to osteoporotics) in clinical settings over long periods of followup, the reproducibility is likely to be poorer than has been reported from specialized research centers (99).

Hip. In 1982 Riggs and associates reported the results of another cross-sectional study where DPA was used to assess changes in BMD with aging (20). They studied the effectiveness of DPA to differentiate patients with hip fracture from normal subjects by measuring changes in the BMD of the proximal femur and spine with aging in 123 normal women and 26 women with hip fractures. In normal women, BMD declined linearly during life by 58 percent in the femoral neck and 53 percent in the intertrochanteric region of the femur. By age 75 years, the authors found that virtually the entire population of aging women had BMD values for the proximal femur that were below their arbitrary threshold for hip fracture. This approach put the entire population of elderly women at risk for hip fracture.

According to Riggs, patients with femoral neck and intertrochanteric fractures were indistinguishable from normal women by differences in BMD at either site (20). Although elderly women with hip fractures had lower values for BMD of the contralateral hip than their peers, the decrease was small and the overlap considerable. For the 26 elderly women with hip fractures, the mean Z-score (deviation in standard deviations from age-adjusted predicted mean) for BMD of the femoral neck was only slightly decreased (-0.50 SD, p less than 0.01), and all individual values were within the age-

adjusted normal range. From these data the authors suggested that although lower BMD of the proximal femur may play a partial role, the occurrence of falls may be a major factor predisposing some but not others in the population of aging women to fracture of the hip (20). This may represent a biased group since Riggs and associates studied ambulatory patients who had survived for at least 1 year after the fracture. According to Cummings, the hip fracture patients chosen for the study may represent a subgroup of otherwise healthy patients who may have had greater bone mass than those who died or were unable to walk (95).

Riggs and colleagues found that the values for BMD of the lumbar spine, midradius, and distal radius sites in the patients with hip fractures did not differ significantly from those for age-comparable normal subjects. By contrast, for 27 additional women ages 51 to 65 years, with nontraumatic vertebral fractures, but not hip fractures, the investigators found a low mean Z-score for BMD of the lumbar spine (-1.92 SD, p less than 0.001). According to Riggs, data from previously published studies and the results of their present study suggest the existence of two distinct osteoporotic syndromes. They designated one form, postmenopausal osteoporosis, characterized by an excessive and disproportionate trabecular bone loss that involves a small subset of women (estimated at 5 to 10 percent) in the early postmenopausal period. It is manifested mainly by vertebral fractures. The other form they designated senile osteoporosis. This syndrome was characterized by a proportionate loss of both cortical and trabecular bone that involves essentially the entire population of aging women (usually older than 75 years) and to a lesser extent, aging men. It is associated with hip fractures or vertebral fractures or both (20). More recently, postmenopausal and senile osteoporosis have been referred to as type I and type II osteoporosis, respectively (100).

Bohr and Schaadt used DPA to determine whether a reduction in BMD of the femoral neck and shaft or of the lumbar spine could be demonstrated in women older than 60 years of age with unilateral fractures of the femoral neck (101). DPA bone

mineral density measurements of the lumbar spine, femoral neck, and femoral shaft in 46 women ranging in age from 60 to 89 years with fractures of the femoral neck were compared with that of 38 healthy women in the same age group. The investigators reported that the BMD of the lumbar spine and femoral neck were not significantly reduced in elderly women with fractures of femoral neck as compared with control subjects. They found the BMD of the femoral shaft, a predominantly cortical bone site, significantly reduced in the fracture group (101). Bohr and Schaadt concluded that the high incidence of femoral neck fracture with increasing age might be explained in part by a reduction in BMC, primarily cortical bone mineral. They added, however, that it is likely that other factors that reduce the strength of bone or increase the tendency in older persons to fall such as dizziness, diminished visual acuity, or muscle weakness, are also of importance (101). In his review of hip fracture studies, Cummings reported that Bohr and Schaadt could have missed a true difference in bone mass because of a small sample size (95). According to Cummings, the study by Bohr and Schaadt may have had insufficient power to detect clinically important differences (type II error).

Cummings studied the role of osteoporosis in the occurrence of hip fractures by critically reviewing case-control studies that have compared the bone mass of patients with hip fractures with that of control subjects (95). He found that the case-control studies suggested that the hips of patients with hip fracture are more osteoporotic than those of other persons of similar age who exhibit no fractures. However, the bone mass differences were usually small and overlapping. While some investigators found patients with hip fractures with substantially less bone at various sites, other investigators have found no significant difference in bone mass between patients and controls (95). According to Cummings, the interpretation of these findings is clouded by fundamental problems in the design and reporting of the studies. He found at least one methodologic problem in each of the 15 studies that could have substantially influenced the results. According to Mazess the results of the 15 studies, reviewed by Cummings, may have been

affected by the investigators choosing an inappropriate region to measure (R. Mazess written communication). But if Mazess is correct in suggesting that 15 studies are capable of introducing such variability, then this strongly suggests that objective interpretation of measurements obtained by different investigators might not be possible. He noted that in only one of the 15 studies did they measure the highly trabecular Wards triangle region in the proximal femur. In that study, Vose and Lockwood reported finding patients with hip fractures with substantially less bone mass at the hip than age-matched subjects (95). Investigators were not "blinded" as to the subjects' status.

Aitken has recently claimed that postural instability is the major determinant for femoral neck fracture, and that generalized osteoporosis, rather than being a prerequisite for fracture, merely determines the type of fracture sustained (102). Aitken conducted a prospective study of fractures of the femoral neck over a 12-month period in order to ascertain the relevance of generalized osteoporosis as determined by metacarpal morphometry. A total of 206 women who sustained fractures of the femoral neck after minor trauma were found to have bone mass measurements (not at the fracture site) similar to those of a control population of the same age without fractures (102). Aitken also reported that 16 percent of the women who incurred fractures had bone mass measurements similar to a group of normal premenopausal women. According to Aitken, although osteoporosis may play some part in the etiology of femoral neck fracture, it is important not to overlook the fact that over 98 percent of these fractures result from falls. He cited a study which reported that among patients aged over 50, women fell four times more often than men and that the incidence of falls rose exponentially with age up to 85 years (102). According to Aitken the results of his study and other data suggested that the absence of generalized osteoporosis was no protection against a femoral neck fracture in elderly women who fall.

To determine if osteoporosis was an important underlying cause of hip fractures

Melton and colleagues recently assessed the relationship between bone density and hip fracture incidence among women residing in Rochester, Minnesota (103). In lieu of a prospective study, the investigators obtained hip fracture incidence rates for specific femoral bone density levels by combining hip fracture incidence data covering several decades with a recent survey of BMD in the same population. BMD measurements at the cervical and intertrochanteric regions of the proximal femur were obtained using DPA. Melton found hip fractures were uncommon among women with femoral bone density greater than 1.0 g/cm^2. They also showed that hip fracture incidence rates increase as bone density decreases below the 1.0 g/cm^2 level. The greater than linear rise in hip fracture incidence observed by Melton was consistent with the reports of Bell, Carter, and Hayes that skeletal resistance to fracture varies in a nonlinear fashion with bone density (77,79).

According to Melton and associates, the cervical fracture incidence rate was 4.0 per 1,000 person-years among all women with cervical BMD less than 1.0 g/cm^2. In women with intertrochanteric BMD less than 1.0 g/cm^2 the fracture incidence was a comparable 3.7 per 1,000 person-years (103). Though the authors concluded that bone mass was an important determinant of hip fractures, they suggested that osteoporosis alone may not be sufficient to produce such fractures, since many individuals remain fracture-free even within the subgroups with the lowest bone density levels. The authors believe that osteoporosis is a necessary but not sufficient cause of age-related limb fractures. According to Melton and colleagues, studies that have matched age and sex have, in effect, matched osteoporosis as well. The failure of bone density measurements to clearly distinguish fracture patients from age-matched controls does not necessarily reflect a lack of association between osteoporosis and the risk of fracture. According to Melton, fracture risk depends on the absolute level of bone density (103). Because the

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BMD measurements were obtained subsequent to the occurrence of the fractures one might regard this as fracture prevalence data in patients with fractures. It does not necessarily reflect future risk.

In an earlier work, Wicks and associates studied patients in an Australian population with fractures of the femoral neck to identify various risk factors associated with the occurrence of those fractures (104). According to Wicks, 73 percent of the 125 patients had a medical condition which could have caused a fall. The conditions included Parkinson's disease or stroke (25 percent), confusion or dementia (23 percent), cataracts or other eye disease (18 percent), and severe diabetic peripheral neuropathy (7 percent). The investigators also found that patients with fractures did not have less bone in the proximal femur than nonfractured control individuals. Examination of the femoral heads failed to reveal a single case of osteomalacia. Wicks concluded that the single most important factor leading to fracture in this population was injury caused by falls and that such injury was frequently associated with other disease processes (104). They suggested that injury causes the sudden failure of a region of the skeleton, which is fracture-prone, by virtue of mechanical factors associated with loss of bone from that site during the aging process (104).

In a recent report of risk factors for injury after a fall, Melton and Riggs reviewed the relative importance of falls versus bone loss as determinants of fracture risk (105). They pointed out that the majority of falls, even among the elderly, do not result in significant injury. They cited a study of 147 falls in a nursing home where only 1.4 percent resulted in a major injury. In another study cited by the authors of 651 falls in a home for the aged, 18 percent resulted in major injury. There were only eight cases of femoral fractures (105). They and many other investigators agree that bone loss predisposes to fractures (105). Because it has been observed that most hip fractures and other age-related fractures are associated with falls, Melton and Riggs concluded that bone loss is a necessary but not a sufficient cause of most age-related fractures (105).

They also believe that some other factor, possibly falls associated with aging are also a necessary but not sufficient cause of age-related fractures.

Physical Activity. In 1982 Krolner and associates reported using DPA bone mineral density determinations to elucidate whether the axial and the appendicular bone mass of middle-aged women with Colles' fractures differed from that of normal individuals (106). The bone mineral measurements were also used to determine whether bone mass was related to the extent of daily physical activity. BMD of the lumbar vertebrae and distal forearms were determined by DPA in 36 patients, aged 50 to 73 years with previous Colles' fracture. None of the patients had symptoms of vertebral compression fractures, and none had femoral neck fractures. The authors found that seven patients with decreased radiodensity of the vertebral bodies had normal lumbar BMD levels, and four patients with normal x-ray findings had lumbar osteopenia determined by diminished BMD. Based on a mean lumbar BMD difference of only 9 percent, the investigators suggested that skeletons of middle-aged women with Colles' fracture compared to age-matched normals have a disproportionately low trabecular bone mass (106). According to Krolner, the Colles' fracture cases represent an easily definable population who may benefit from prophylactic measures against bone loss. In 1974, after a 10-year followup of 109 women who suffered a radial fracture, Gay reported that a subsequent osteoporotic-related fracture occurred in 33 (30 percent) of the women. He came to a similar conclusion that fractures of the distal radius may be considered as a "marker" for women at risk of subsequent fractures (107). Nordin has recently reported that wrist, spine, and hip fractures are inter-related. The occurrence of one type of fracture usually indicates an increased risk of subsequent fracture at other sites. Nordin found that patients who have had a wrist fracture incur a significantly increased risk of vertebral and/or femoral neck fractures than age-matched controls (19).

According to Krolner, the DPA bone mineral density values of the lumbar vertebrae had a positive correlation to the working capacity (bicycle ergometer) of the patients

(106). Based on that relationship, the investigators suggested that the bone mass of the axial skeleton reflects the extent of the daily physical activity of the patients and that physical activity modulates the rate of bone loss from the vertebrae in middle-aged women. The findings of Krolner and associates suggested that physical exercise be considered as a prophylactic measure against vertebral bone loss in middle-aged women with Colles' fracture. An earlier epidemiological study by Chalmers and Ho also emphasized physcial activity as a possible prophylactic measure against senile osteoporosis (82). Using the incidence of hip fractures as an indication of senile osteoporosis, the investigators found the occurrence of the disease to vary greatly in different racial groups. They also found that the sex incidence also varied. According to Chalmers and Ho these differences could not be attributed to hormonal state or to the amount of dietary intake of calcium. They suggested that the differences in the incidence of hip fractures were due to the living standards of the different countries and the degree of physical activity undertaken by the different populations and sexes (82).

In 1983 Krolner and associates reported on a subsequent study that used DPA measurements of the lumbar spine in women, with a mean age of 61 years, to determine whether physical exercise could prevent involutional bone loss (108). The skeletal effects of physical training were studied in a program involving 27 of the 31 women with previous Colles' fracture of the forearm. The patients were maintained on their usual diets. Calcium supplements were not given and all medical treatment was continued. The investigators found the lumbar spine BMC of the group (N=13) exercising for 1 hour twice weekly for 8 months increased by 3.5 percent, whereas that of the control group (N=14) decreased by 2.7 percent. The authors found the difference between these changes was significant (p less than .005). However, the difference in the measurements between the beginning and the end of the study for both groups was smaller than the precision value of the DPA technique. According to the authors the results suggested that physical exercise can inhibit the involutional bone loss from the axial skeleton in

middle-aged women and lead to a net gain in axial bone mass (108). Krolner concluded, that the data support the hypothesis that involutional bone loss reflects an adaptive response to decreased physical activity, making decreased mechanical stimulation with increased age an important pathogenetic factor in osteoporosis (108).

Similarly, Rogers after reviewing studies on exercise and other factors affecting BMC concluded that the high frequency of osteoporosis in more advanced age may result largely from diminished activity during later life (75). According to Rogers, even in chickens, lack of exercise produces osteoporosis. He suggested that osteoporosis, rather than being caused physiologically by the aging process, is probably brought on by the lifestyles of older people. Also, he would include hormonal imbalance and inadequate diet as other factors which may be involved (75). In a recent cross-sectional study, Kanders and associates examined the relationship between calcium and exercise in 60 normal young women (109). They performed nutritional studies and examined the women's exercise patterns with historical data and prospectively by pedometer. The investigators found that women who had high activity patterns did not have an increased bone mass unless there was evidence that their calcium intake was above the current recommended dietary allowance (RDA). Kanders suggested that it was possible that calcium is an important cofactor for the exercise effect, and in treatment, but that by itself it is not effective.

Cummings and colleagues have reviewed the limited literature regarding the effects of exercise on the bone mass of postmenopausal women (32). They concluded that although some of the studies found a beneficial effect, the role of physical activity is inconclusive and not well studied. The inconclusive results of studies of the effect of exercise on postmenopausal women do not, however, imply that exercise is not important in preventing osteoporosis. Lifelong physical activity has been shown conclusively to increase BMC (110). Recent research in exercise and BMC has focused, however, on the decreased BMC found in young active amenorrheic women (111). In 1984, Drinkwater and

associates reported using DPA bone mass measurements of the vertebrae to determine whether the hypoestrogenic status of 14 amenorrheic athletes was associated with a decrease in regional bone mass (112). They found amenorrheic runners had 14 percent less vertebral mineral based on BMD measurements than a matched group of regularly menstruating runners. According to the investigators the BMD of the amenorrheic women, who were in their mid-20's, corresponded to that of 50-year-old women, as did their endogenous estradiol levels. Drinkwater and colleagues concluded that the results of the study did not negate the value of exercise in maintaining skeletal integrity but rather pointed out the interaction between estrogen and exercise in their effect on specific skeletal areas (112).

In a recent Australian study, Pocock and coworkers demonstrated that BMD of the femoral neck and lumbar spine in women is significantly related to variations in the level of physical fitness (113). In their study of 84 normal Caucasian women, femoral neck and lumbar spine BMD measurements by DPA were significantly correlated with fitness (predicted maximal oxygen uptake) as well as age and weight. In the 46 postmenopausal subjects, fitness was the only significant predictor of femoral neck BMD. Both weight and fitness predicted the lumbar BMD (113). According to the authors, physical fitness in this normal group accounted for 23 percent of the variation in femoral neck BMD. Pocock suggests that increased physical fitness may increase bone mass at the sites of clinically important fractures in osteoporosis and may be a useful modality in prevention of fractures at these sites (113).

Safety of DPA

Radiation exposure is always a concern with any procedure utilizing radiation sources. And while DPA is a noninvasive technique, it does involve patient exposure to radiation. Dosimetry measurements performed in the laboratory of Wahner and

colleagues at the Mayo clinic showed that a dual photon scan of the lumbar spine with a 1.5 Ci Gd-153 source gave a peak skin dose of 18 mrad with a scatter dose to the eyes of 5 mrad and to the gonads of 8 mrad (1).

Other investigators have reported similar findings. According to Mazess, the radiation dose from dual photon measurements is under 15 to 20 mrem (13). Krolner and Pors Neilsen calculated a skin dose over L3 as 10 mrad for DPA (14). They found the total dose to the ovaries to be less than 2 mrad, and the bone marrow dose less than 0.2 mrad. The radiation exposures are as low as those received from any diagnostic x-ray or nuclear medicine procedure in use today. For comparison, a typical chest x-ray exposes a patient to 20 to 40 mrad. Some investigators, such as Krolner and Pors Nielsen ensure correct positioning of the patient over the source by radiological examination and palpation (14). Besides vertebral levels, the radiograph identifies fractures and osteophytes. These routine spinal roentgenograms raise the total radiation exposure of this technique. A lumbar spine series involves an exposure of 600 mrad, with a large percentage of gonadal radiation (2).

Recently, the Department of Radiology at The Johns Hopkins University School of Medicine assessed the patient dose delivered by a dual photon absorptiometer. The system consisted of an encapsulated 1.0 Ci source of Gd-153 located 9 cm below the patient examination tabletop. Patient dose which is highest at the skin entrance surface is dependent on scan speed and line spacing. The values measured by the Department of Radiology were 5.3 mrad for the standard scan (intermediate dose) and 1.6 mrad for the survey scan (least dose). According to the investigators, these are exceptionally low-dose values that are consistent with the manufacturer's specified skin dose of less than 30 mrem. The Department of Radiology at the Johns Hopkins University School of Medicine concluded that the radiation risk associated with doses of this magnitude can be considered to be negligible (T. Beck, written communication).

DPA operators/owners need to check the current status of Nuclear Regulatory

Commission (NRC) or State licenses, which usually have to be amended before the manufacturer or other supplier will ship the Gd-153 source. Under new NRC regulations, DPA may be used by Group VI licensees whose physicians complete 8 additional hours of training (15).

DISCUSSION

The measurement of bone mass is obviously an important tool in the study of metabolic bone diseases, particularly osteoporosis. Much current interest is centered on the recent technique of DPA. This interest is a result of the applicability of the DPA technique to the spine and hip, sites of important osteoporotic fractures. Presently, DPA has utility in clinical research in studying the natural history of primary osteoporosis in large populations and in evaluating preventive and therapeutic regimens (as in the dose-response effect of estrogen). While DPA is capable of measuring bone mineral density and has advanced our knowledge of bone disease in general, its role in the management of the individual patient is uncertain.

It would be advantageous to be able to prospectively identify those women who are at risk of developing osteoporotic fractures in order to direct treatment to those at greatest risk. As a screening test for osteoporosis in perimenopausal women, this application of BMC measurements is suggested to have potential utility. Once established as a screening tool it could provide a rational basis for treating afflicted individuals or preventing osteoporosis. Although the technology to noninvasively measure bone mineral density with DPA is currently available, the ability of such measurements to identify those individuals who will subsequently have fractures has not yet been shown. There has been no prospective study demonstrating that the noninvasive measurement of bone mass can identify which patients will suffer hip, Colles', or vertebral fractures. In their 1984 review of the various noninvasive methods for bone

mineral measurements, Wahner and colleagues concluded that there was no optimal technique available for mass screening for early osteoporosis (1). The American College of Physicians' Health and Public Policy Committee recently reviewed various radiologic methods for measuring BMD, including DPA, but made no recommendation about the use of these tests in routine screening for osteoporosis (2). To predict an individual's fracture risk it would be necessary to study large population cohorts of women from various age groups and relate their specific bone measurements to prospective fracture incidence data collected over a sufficient period of time. From fracture incidence data the risk ratio could provide an estimate of risk. This type of study would enable investigators to determine whether or not it is possible to predict the risk of fracture from the initial bone density measurements. It is important to remember that a patient's bone mass measured before or at menopause may indicate whether she has low or high bone mass for her age. It will not necessarily indicate whether she will fall into the high-risk group 10 to 15 years later, when fractures begin. The contribution of bone mass at maturity versus subsequent rates of loss is still largely unknown (29). Moreover, there exists a controversy regarding the selection of a screening site. While many investigators consider BMD measurements of the actual fracture site (spine and hip) paramount, others argue that fracture risk prediction and screening can be accomplished by appendicular (trabecular) BMD measurements.

According to Grubb and coworkers, measurements of distal radius (5 mm site) bone density establish an appendicular site at which bone density losses are closely correlated with vertebral bone loss in both patient and normal populations (114). Grubb suggests that measurements at the distal radius are as good as the measurements at the spine itself for predicting vertebral fractures. This is in contrast to the reported low correlation in patient studies of bone density of radial sites to lumbar vertebral density (3,26). According to Mazess, 30 to 40 percent of patients at risk will be missed with measurements on the distal radius or the os calcis (13). In disagreement with Mazess

regarding the poor predictive values from SPA measurements, Wasnich and colleagues believe that fracture risk prediction and screening can be accomplished by appendicular (trabecular) BMD measurements (115). Recently, they found the os calcis as a suitable site for screening and the single, most clinically useful site for routine risk evaluation of perimenopausal women. However, their risk prediction data does not include any vertebral fractures incidence. Only vertebral fractures prevalence and only one hip fracture are included.

Initially, researchers used DPA bone mineral measurements in attempts to find a specific level of bone density that clearly distinguished patients with vertebral osteoporosis from those without. Those studies, including the work of Riggs and associates and Krolner and Pors Nielsen, have been largely unsuccessful (3,86). Riggs et al. found that in a comparison of spinal BMD of patients with osteoporosis with that of an age- and sex-adjusted normal range, only about 60 to 70 percent of patients with osteoporosis have values below the fifth percentile of normal (3). Krolner and Pors Nielsen found the overlap so large between patients with clinical spinal osteoporosis and age-matched normals, that the majority of patients were indistinguishable from the age-matched normals (86). Cohn and associates used a multiple logistic regression model to discriminate osteoporotic women on the basis of spinal BMD determined by DPA (116). They reported a correct classification in only 55.6 percent of the total osteoporotic subjects in the 50-59 year age group. According to Wahner, no clear bimodality exists in the distribution of bone mineral in normal persons and in patients with osteoporosis when the latter group is defined as those persons in whom spinal compression fractures are present (117). Because of the considerable overlap between the groups, and the fact that many individuals with low bone mass do not sustain fractures, Kanis concluded that bone mass may not be the major determinant of fracture and other factors such as trauma need to be considered (118).

Data from a recently published abstract suggest that bone mass is an important

determinant of vertebral fractures (119). From a population-based study of the relationship between osteoporosis and vertebral fractures Melton and colleagues at the Mayo Clinic, calculated the prevalence rate of vertebral fractures at various levels of spinal bone mineral. They found that below a bone mineral threshold of 1.40 g/cm^2 the prevalence rate increased as spinal bone mineral decreased. The possibility of a dose-response relationship would strengthen the argument for a causal relationship between bone mineral and vertebral fractures (119). While there is ample evidence to suggest that people with fractures have low bone mass,a fracture incidence data are still needed to determine the risk ratio as an estimate of future risk.

According to Cummings and colleagues, the assumption that people with the lowest bone mass are the most likely to suffer fractures appears to hold true for vertebral fractures (32). Investigators such as Riggs and colleagues who were unable to clearly distinguish patients with vertebral osteoporosis from those without, consistently found less trabecular bone, on average, in women with vertebral fractures (3). From their study of risk factors for injury after a fall, Melton and Riggs concluded that a reduction in spinal bone mass is the primary determinant of who will suffer vertebral fractures (105). According to Cummings, these findings suggest that DPA measurements of vertebral bone mineral density may be a useful way of identifying women with the greatest risk of vertebral fractures (32). The authors recommend that the use of DPA for predicting vertebral fractures should be tested in prospective studies before they are advocated for widespread use or before they are employed as a basis for recommending specific types of preventive therapy (29). While other investigators agree that, ideally, the accuracy of prediction should be demonstrated prospectively, they have attempted to find better ways of determining the magnitude of risk from cross-sectional studies in the absence of prospective studies.

It is important to consider that the ultimate benefit (fracture risk identification and guide to treatment) of early diagnosis of spinal osteoporosis by DPA measurements

will depend on the clear establishment of safe and effective treatments. While it has been shown that postmenopausal estrogen therapy currently appears to be the most effective single method for preventing bone loss and fractures in women, its use is not without risk (32). In determining whether estrogen treatment should be initiated, the physician and the menopausal patient must make a judgment based on a reasonable assessment of the relative benefits and risks to the individual patient. Varied symptoms are associated with and have been attributed to the menopause. Moreover, proposed uses for estrogen therapy in the postmenopausal period have included the prevention of coronary heart disease but this use remains controversial (48). According to Cummings and associates, et al. there is mounting evidence that estrogen therapy protects against coronary heart disease, but Haber believes the issue must currently be regarded as unsettled (32,48). They both agree that if additional evidence confirms that estrogen substantially protects against coronary heart disease, then preventing coronary heart disease would become the major indication for long-term estrogen therapy (32,48). However, it is known that postmenopausal estrogen therapy increases the risk of endometrial cancer (56). In addition to the problems of carcinoma of the uterus and possibly the breast, estrogen replacement has been associated with an increased incidence of gallbladder disease and hypertension (46). According to Johnston, problems with patient compliance and acceptance, particularly with estrogen and progesterone combinations which induce repeated episodes of bleeding related to drug withdrawal, should be noted. Cummings indicates that many of the patients on estrogen therapy discontinue the therapy within a year. There is also a high percentage of hysterectomies in this group as well, he adds (personal communication). In deciding whether to use estrogens after menopause, women and physicians may consider other factors to be at least as important as prevention of osteoporotic fractures.

The epidemiology and natural history of vertebral fractures have not been well described. Vertebral fracture may be classified either as partial vertebral deformity,

which is the partial loss of height of the anterior edge or middle section of a vertebral body, or a complete compression fracture, which is the collapse of the entire vertebral body (32). Kleerekoper and associates reviewed the various reports of vertebral fracture incidence and found that in white women over age 45 who have normal spine films, the annual incidence of complete vertebral fractures has been estimated to be about 2.3 per 1,000 women and about twice as high in women with apparently reduced spinal density (120). From a spine x-ray survey of elderly women, Marshall and associates reported that 62 percent of the 50 women between ages 65-75 showed some degree of vetebral deformity (121). However, they found that only 6 percent had collapsed vertebrae. Jensen and associates found that 5 percent of 70-year-old Danish women had complete compression fractures and an additional 18 percent had partial deformities of at least one vertebra (122). Though vertebral body deformities are prevalent in the elderly, more research is needed to determine how much pain or disability is attributable to this manifestation of osteoporosis.

Vertebral fractures occur more or less spontaneously or as the result of very minimal trauma in the course of daily living. Patients with spinal osteoporosis display considerable individual variation both in the severity of their symptoms and in subsequent fracture history. It is well recognized that many vertebral fractures are asymptomatic and are often detected only incidentally on chest or spine films long after they have occurred (120). When pain occurs, it usually subsides after several days to weeks, and by 4 to 6 weeks patients may be fully ambulatory and able to resume their normal activities. Patients with vertebral fractures are usually managed with rest and nonnarcotic analgesics. Most patients have disappearance or marked diminution of pain between episodes of vertebral body collapse. There may be intervals of several years between fractures (123). Recurrent episodes of vertebral fracture lead to progressive loss of height and increasing deformity that can cause a kyphotic "dowager's hump" posture and may lead to chronic back pain (32). A relatively small proportion of patients

develop the full crush fracture syndrome with wedging of the vertebral body and disruption of the cortex (124). While compression fractures (collapse fractures) of the vertebrae can produce severe pain, Cummings and coworkers believe that the amount of back pain and disability attributable to most vertebral fractures is unknown (32). According to Cummings there is insufficient information of the morbidity and functional consequences of vertebral fractures to justify routine screening of all postmenopausal women for that condition (99).

Recently, investigators have also applied the DPA technique of bone mineral density measurements in studies to distinguish those with a high risk of hip fracture from those with a low risk (20,101,103). Two related issues have emerged in this area of study. The first pertains to the role of osteoporosis in the occurrence of hip fractures. Investigators such as Melton and colleagues believe that age-related bone loss (osteoporosis) is a major determinant of hip fracture incidence (103). This assumption is based on the decline of BMD with age, its correlation with bone strength, and the occurrence of fractures as a function of bone strength as well as the degree of trauma. The failure of DPA bone density measurements to clearly distinguish fracture patients from age-matched controls has prompted other investigators to conclude that in addition to low bone mass, which is nearly universal among the very elderly, other factors are important in determining who will experience a hip, or Colles' fracture. (95,101,102,104). According to Bohr and Schaadt, the high incidence of hip fractures with increasing age might be explained in part by a reduction in BMC, but they concluded that other factors that reduce the strength of bone or increase the tendency to fall are also of importance (101). Wicks concluded that the single most important factor leading to fracture in the Australian population studied was injury caused by falls and that such injury was frequently associated with other disease processes. Wick and colleagues suggested that injury causes the sudden failure of a region of the skeleton which is fracture-prone by virtue of mechanical factors as well as the loss of bone from that site during the aging

process (104). Since most hip and Colles' fractures occur as the result of falls, Cummings and colleagues suggested that the tendency to fall or the inability to protect oneself from injury during a fall may be important in determining who will fracture a hip or wrist. They included microfractures and bone geometry as other characteristics of bone that may be important in determining the susceptibility of a bone to fracture (32).

Although the recent findings by Melton and associates show that it is reasonable to consider bone mass as an important determinant of the age-related hip fracture incidence, the findings did not establish the ability of DPA bone mass measurements of the hip to distinguish those with a high risk of hip fracture from those with a low risk (103). This second issue remains controversial and unproven. According to Melton, the failure of bone density measurements to clearly distinguish fracture patients from age matched controls does not necessarily reflect a lack of association between osteoporosis and the risk of fracture. If bone mass does not differ in patients with hip fractures and other elderly persons, then measurements of bone mass would be of little or no value in predicting which elderly patients are likely to incur a hip fracture. Measurements of bone mass might not be a reliable way to identify those patients at greatest risk of hip fracture. According to Melton and associates, more than 85 percent of the women 65 years and older in the general population are at risk because their BMD levels are less than 1.0 g/cm^2 (103). That being the case, treatment methods could be undertaken without the use of individual DPA bone mass measurements. It is not certain what value DPA measurements of bone will have in identifying women at greatest risk of hip or Colles' fractures. This application of the DPA method needs further clinical investigation before it is advocated for widespread use or before it is employed as a basis for recommending specific types of preventive therapy (29).

The use of DPA bone mineral measurements as an index of fracture risk is based on the assumption of an inverse correlation between the occurrence of fractures and the amount of bone mass. Although a high correlation exists between compression strength

and mineral content, other factors provide resistance to compressive stress. Physical activity may exert an effect on the trabecular structure of bone apart from its mineral composition (75). According to Bell and others, vertebral strength depends not only on BMC, but also on the trabecular structure of the vertebral body, something that cannot be measured separately by DPA (77,80).

According to Ruff and Hayes, the geometric distribution of bone tissue, together with its material properties, is critical in determining the structural strength and rigidity of the whole bone. They conclude that the most critical skeletal age changes may not be those that occur in BMC or BMD, but rather geometrical properties and material characteristics other than density. The investigators suggest that this may explain the failure of DPA measurements to clearly distinguish between high- and low-risk fracture risk individuals (80).

Although the DPA method makes it possible to obtain bone density measurements from the axial skeleton, it cannot measure purely trabecular bone. The DPA technique measures integral vertebral bone consisting of a mixture of low-turnover compact bone in the cortex, pedicles, transverse processes, and vertebral end plates. It also measures high-turnover cancellous bone in the vertebral body (55). The dense outer shell of the vertebrae (cortex) has been found to make a substantial contribution of 30 to 40 percent to the DPA measurement (7). The sensitivity of a technique that measures an integral of compact and cancellous bone may be low due to inclusion of low-turnover compact bone and extra-osseous material such as osteophytes or aortic calcification. This may place DPA measurements at a theoretical disadvantage if the measurement of purely trabecular bone provides a better method of quantifying change in a metabolic bone disease than does an integrated measure of both cortical and trabecular bone (2).

The recent findings of Hayes and Gerhart that the cortical shell contributes very little to the overall strength of the vertebral body would support the need to distinguish between cortical and trabecular components in the spine (72). Using quantitative

computed tomography, Hayes and Gerhart were able to predict the apparent density (g/cm^3) of trabecular bone in the vertebral centrum. They found that the vertebral density and cross-sectional area could be used to predict vertebral load failure (fracture) under test conditions. Hayes and Gerhart recommended clinical studies to determine whether these measurements will provide a useful tool for identifying individual patients at increased risk for spontaneous vertebral fracture (72).

A second clinical application proposed for the DPA technique has been the use of DPA measurements to monitor the effectiveness of treatment. This could apply to the treatment of individuals with established osteoporosis and also to those receiving preventive regimens. According to Lindsay, there is no current evidence that serial bone mass measurements need to be performed in patients receiving adequate estrogen, since studies indicate that more than 90 percent of these patients will be protected against bone loss (34).

Before the DPA technique is considered for general clinical practice it must be determined whether the precision of the technique is adequate to measure bone mass changes in time in one individual. The factors which determine the ability to detect changes in individual patients depend on the confidence in the measurement (confidence being inversely proportional to the coefficient of variation), the rate of change to be measured, and the duration of the study (125). The reproducibility of DPA measurements has been documented by a number of researchers, who found that the coefficient of variation was less than 5 percent (11,12,14,36,63). While some investigators have reported a 2 and 3 percent coefficient of variation for DPA, these calculations of reproducibility will tend to underestimate the reproducibility of the technique applied to individuals in nonresearch settings over prolonged periods of followup. Nevertheless, according to Kanis, a patient would have to be studied for 4 to 8 years to detect significant bone loss if the rate of bone loss was 1 percent per year and the coefficient of variation was between 2 and 5 percent (125). Age-related bone loss in the spine is about

1 percent per year in normal postmenopausal women. If the rate of bone loss was greater (2-3 percent), significant bone loss could be determined in less time, but probably not less than in 3 years which would still make the DPA technique unsuitable for serial measurements. According to Johnston, a high degree of precision in the bone mass measurement is necessary for repeated measurements of small degrees of change, and such precision is difficult to attain, even in the best controlled laboratory environment (29). According to Ott and others, until more sophisticated methods of improving the reproducibility are developed, these tests will be valuable in studying large groups of patients, but will not be as helpful in individual cases (62,91,98).

Advice and comments concerning the safety and clinical effectiveness of DPA have been sought from groups and organizations within and outside of the Federal Government. An announcement of this assessment appeared in the Federal Register notice of October 26, 1984 (126). On June 20, 1985, before the Subcommittee on Aging of the Committee on Labor and Human Resources, United States Senate, the National Institutes of Health (NIH) through the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases (NIADDK) stated that it was a research imperative to develop methods for measuring bone density. Besides diagnosis these methods should enable early identification of bones most vulnerable to fractures and provide a measure by which to evaluate the effectiveness of new therapies (40). According to NIADDK while several noninvasive methods for measuring bone density have been developed, and DPA is among the promising techniques, presently, no existing techniques can adequately discriminate early in the disease process between normal and osteoporotic individuals (40). The NIADDK recommended long-term clinical trials of various specific patient populations in statistically significant numbers 1) to provide estimates of risk, and 2) to determine the optimal regimen to prevent bone loss and fracture.

At that same hearing on osteoporosis, the National Institute on Aging (NIA) stated that there is a need for better ways of identifying persons at high risk of fracture, since

those individuals could be expected to benefit most from treatment (37). Because it is still unclear which persons would benefit from which treatments and at what dosages and schedules, additional research and clinical trials are needed to develop the current state of knowledge regarding prevention and treatment of osteoporosis for specific individuals or groups. The American College of Obstetricians and Gynecologists (ACOG), in their statement before the Subcommittee on Aging indicated that presently, there are no tests to identfy which women are at risk for developing osteoporosis (28). The College recommended that the physician determine bone loss by aborptiometry in their diagnosis of osteoporosis. The College also recommended estrogen replacement therapy as the most effective way of slowing bone loss for those women who are at risk of developing osteoporosis (28).

Prior to the June 20, 1985 Senate Hearing on osteoporosis, the NIH Consensus Development Conference on Osteoporosis was held on April 2-4, 1984 (33). At that conference data were presented which showed that none of the noninvasive techniques for measuring bone mass were able to discriminate significantly between normal and osteoporotic individuals. None of the techniques for currently quantitating bone mass, including DPA, can definitively predict the individual at significant risk for osteopososis prior to the occurrence of fracture. The Consensus Panel concluded that osteoporosis was a major public health problem requiring additional research on the biology of human bone, defining individuals at risk, and developing safe, effective, low-cost strategies for fracture prevention. The panel recommended studies to develop accurate, safe, inexpensive methods for determining the level of risk for osteoporosis in an individual, to establish early diagnosis, and to assess the clinical course of the disease (36).

According to the Food and Drug Administration (FDA), DPAs are being marketed under Section 510(k) of the Medical Device Amendments to the Food Drug and Cosmetic Act. FDA has found DPA sufficiently similar in terms of safety and effectiveness to be considered "substantially equivalent" to single photon absorptiometers that were being

marketed prior to enactment of the Medical Device Amendments of May 28, 1976 to the Food, Drug and Cosmetics Act. Bone densitometers have been proposed for classification as Class II (Standards) devices.

Through its Clinical Efficacy Assessment Project, The American College of Physicians published a policy statement on radiologic methods to evaluate BMC in June 1984 (2). The College concluded that all methods of BMC measurement result in significant overlap between diseased and normal populations. They stated that the ultimate benefit of early diagnosis of metabolic bone disease will depend on the clear establishment of safe and effective treatments. The College believes that measurements of bone mineral content have greater utility in following the course of a disease process or assessing the effect of therapy than in establishing a diagnosis. According to the College neither CT nor DPA accurately predicts tendency to fracture and the relative value of these two techniques has not been completely established.

The Orthopaedic Research Society strongly supports continued research in the development of noninvasive techniques for understanding metabolic bone disease. The Society suggested that the research examine the precision, accuracy, sensitivity, cost, availability, and relevance to underlying metabolic bone disease of each of the techniques currently under study. The Society also suggested a workshop directed at the understanding of the surveillance of bone disease.

It is the opinion of the Society of Nuclear Medicine that bone mineral density studies should become part of the workup of patients with osteoporosis and that DPA is the technique of choice at this time. According to the Society, information on BMD provided by DPA is needed to identify patients in need of treatment for osteoporosis. They suggest it also be used to monitor patients for treatment effectiveness, to exclude patients resistant to a specific treatment regimen, and to identify the end of the effectiveness of the treatment.

A response from the American College of Nuclear Physicians concluded that

osteoporosis can be detected at its earliest stages by DPA measurements of the vertebral spine. According to the College, to postpone or prevent the problems of insidious progressive osteoporosis, early detection and screening by bone mineral analysis of the lumbar spine by DPA is critical. The College also recommends the use of repeated measurements by DPA to give information on the rate of bone loss, allow assessment of the activity of the disease, and determine the effect of the therapy.

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SUMMARY

DPA is a noninvasive radiologic technique used to measure BMD in the lumbar spine and hip. The DPA technique for measuring BMD is based on measurements of radiation transmission of two separate photon energies through a medium consisting of two different materials, bone and soft tissue. The difference in photon absorption between bone and soft tissue allows for the calculation of the total bone mineral found in the scan path. With DPA the amount of bone mineral measured represents the total integrated mineral (cortical and trabecular) in the path of the beam.

The measurement of bone mass is obviously an important tool in the study of metabolic bone diseases, particularly osteoporosis. While DPA is capable of measuring bone mineral density and has advanced our knowledge of bone disease in general, its impact on the management of the individual patient is equivocal. Although the technology to noninvasively measure bone mass with DPA is currently available, the ability of such measurements to predict who is at risk of subsequently developing fractures (screening) has not yet been shown. Moreover, there exists a controversy regarding the most appropriate bone site to use for screening patients.

Studies with DPA that attempted to find a specific level of bone density that distinguished patients with vertebral osteoporosis from those without have been largely unsuccessful. Recent studies to distinguish those with a high risk of hip fracture from those with a low risk have also been unsuccessful. While recent studies indicate that a reduction in spinal bone mass is the primary determinant of who will suffer vertebral fractures, other studies have prompted investigators to conclude that in addition to low bone mass, other factors such as trauma or falls are important in determining who will experience a hip or Colles' fracture.

DPA measurements of vertebral bone mass may be a useful way of identifying women with the greatest risk of vertebral fractures, but it is not certain what value DPA

measurements of bone will have in identifying women at greatest risk of hip or Colles' fractures. These methods for predicting fractures should be tested in prospective studies before they are advocated for widespread use or before they are employed as a basis for recommending specific types of therapy.

A second clinical application proposed for the DPA technique has been the use of DPA measurements to monitor the effectiveness of treatment. A high degree of precision in the bone mass measurement is necessary for repeated measurements of small degrees of change, and such precision is difficult to attain. Presently, the suitability of the DPA technique for monitoring the effectiveness of treatment is controversial.

The ultimate benefit of early diagnosis of osteoporosis also depends on the clear establishment of safe and effective treatments. While treatment with estrogens has been found to be effective, its risks and benefits need to be assessed. Most other therapies are considered investigational.

Investigators have not distinguished between the use of DPA in clinical research and its role in day-to-day practice. DPA needs to undergo further clinical investigation before it can be recommended for general clinical use.

According to the FDA, DPAs are allowed to be marketed pursuant to Section 510(k) of the Medical Device Amendments. FDA has found DPA sufficiently similar in terms of safety and effectiveness to be considered "substantially equivalent" to single photon absorptiometers that were being marketed prior to enactment of the Medical Device Amendments of May 28, 1976 to the Food, Drug and Cosmetics Act.

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APPENDIX III - Public Health Service Assessment of Radiographic Absorptiometry for Measuring Bone Mineral Density - 1987

Health Technology Assessment Reports, 1987

Radiographic Absorptiometry for Measuring Bone Mineral Density

Number 2

NATIONAL CENTER FOR HEALTH SERVICES RESEARCH AND HEALTH CARE TECHNOLOGY ASSESSMENT

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service

FOREWORD

The Office of Health Technology Assessment (OHTA) evaluates the safety and effectiveness of new or unestablished medical technologies that are being considered for coverage under Medicare. These assessments are performed at the request of the Health Care Financing Administration (HCFA). They are the basis for recommendations to HCFA regarding coverage policy decisions under Medicare.

Questions about Medicare coverage for certain health care technologies are directed to HCFA by such interested parties as insurers, manufacturers, Medicare contractors, and practitioners. Those questions of a medical, scientific, or technical nature are formally referred to OHTA for assessment.

OHTA's assessment process includes a comprehensive review of the medical literature and emphasizes broad and open participation from within and outside the Federal Government. A range of expert advice is obtained by widely publicizing the plans for conducting the assessment through publication of an announcement in the Federal Register and solicitation of input from Federal agencies, medical specialty societies, insurers, and manufacturers. The involvement of these experts helps assure inclusion of the experienced and varying viewpoints needed to round out the data derived from individual scientific studies in the medical literature. After OHTA receives information from experts and the scientific literature, the results are analyzed and synthesized into an assessment report. Each report represents a detailed analysis of the safety, clinical effectiveness, and uses of new or unestablished medical technologies considered for Medicare coverage. These Health Technology Assessment Reports form the basis for the Public Health Service recommendations to HCFA and are disseminated widely.

Individual reports are available to the public once HCFA has made a coverage decision regarding the subject technology. OHTA also publishes compilations that contain all assessment reports submitted to HCFA in a given calendar year.

OHTA is part of the National Center for Health Services Research and Health Care Technology Assessment (NCHSR), Public Health Service, Department of Health and Human Services.

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ABSTRACT

Radiographic absorptiometry (RA) is a noninvasive radiologic technique involving a computer-assisted densitometric measurement of the x-ray image of bone. Mineral density analyses are based on phalangeal scans of pairs of exposed radiographs with an aluminum alloy reference wedge included in the image field. The technique can achieve a precision of 2-4 percent with a radiation dose of 10-100 mrad. While RA is capable of measuring bone mineral density and has advanced our knowledge of bone disease in general, its impact on the management of the individual patient is equivocal. Studies with RA that attempted to find a specific level of BMD that distinguished patients with osteoporosis have been largely unsuccessful. Also, the ability to predict who is at risk for subsequently developing fractures of the spine and hip has not yet been shown. Studies with RA measurements show a large scatter in the data that precludes a reliable prediction of bone mineral at one site based on measurements at another site in a particular individual. Radiographic absorptiometry needs to undergo further clinical investigation before it can be recommended for general clinical use.

PUBLIC HEALTH SERVICE REASSESSMENT OF RADIOGRAPHIC ABSORPTIOMETRY FOR MEASURING BONE MINERAL DENSITY

1987

INTRODUCTION

Radiographic absorptiometry (RA) is a noninvasive radiologic technique involving a computer-assisted densitometric measurement of the x-ray image of bone (1). Mineral density analyses are based on phalangeal scans of pairs of lightly exposed radiographs taken at different kilovoltage and exposure settings. An aluminum alloy reference wedge, which allows the computer to compensate automatically for any between-film differences in exposure, kilovoltage (kVp), filtration, film type, and film processing conditions, is included in the image field. A computer-controlled optical densitometer scans the x-ray image with a light beam. A photocell converts the light, modulated by the images, to an electrical signal that is digitized and sent to the computer for analysis and determination of bone mineral density (BMD). The system is designed to compare the findings from the patient's hand-wrist radiographs with normal values of phalangeal bone size and BMD determined from age-and sex-matched controls (2). In RA, bone mineral mass is determined and expressed as BMD (mineral concentration) by accounting for bone size (bone image area). Measurements of bone mineral by RA have been used to provide an index of skeletal status, predominantly in the assessment of renal osteodystrophy and osteoporosis.

Described in detail in 1979, RA is considered a simple, widely available, and relatively inexpensive bone mineral measurement technique (1). Similar techniques, where the optical density of bone on x-ray films is obtained under standardized conditions and used as a quantitative indicator of bone mineral content (BMC), have been used for many years (3). RA was developed in an attempt to circumvent some of the inherent limitations in the use of an x-ray image to measure BMD. Methods that measure BMD from an x-ray image have been referred to as photodensitometry, aluminum equivalency, radiographic densitometry, and radiographic absorptiometry.

According to some investigators, these methods have technical problems relating to radiographic technique and methods of film processing that limit their use (4,5). However, according to the position paper on radiologic methods to evaluate BMC from the Health and Public Policy Committee of the American College of Physicians, recent advances such as radiographic absorptiometric techniques may have reduced these problems (6).

The technique of RA utilizes image scans of the second, third, and fourth phalanges from two lightly exposed left-hand radiographs, one taken at 40-50 kVp, and the other at 50-60 kVp. An aluminum alloy reference wedge is radiographed alongside the index finger. Radiographs can be taken on any type of film without intensifying screens and with any x-ray machine. Charges for a pair of hand radiographs commonly range from $96-$160 and take from 5-10 minutes.

Using a computer-controlled scanning microdensitometer the aluminum alloy reference wedge image (on the x-ray film) is scanned. From the optical density readings (grey level) of the wedge image, the linear absorption coefficient of the wedge, and the background optical density due to film base emulsion, chemical fog and scatter are determined (2). Using the computer, these quantities are used to determine correction terms for differences between films due to different x-ray machines, kilovoltage, prefiltrations and exposure settings, film types, and film processing.

Subsequently, the scanning process is repeated for each phalangeal bone image. The scanning microdensitometer transmits a narrow beam of light through the film, traversing each bone image slice by slice. Successive parallel paths across the image of the whole phalangeal bone are scanned. Typically, 25-30 parallel scans, 1 mm apart, cover an adult middle phalangeal bone with about 200 data points per scan line (2). At the end of each scan line, the edge detection algorithm of the computer recognizes the bone edges, measures the local bone width, and generates a soft-tissue baseline. According to Colbert and Bachtell, this method computes mostly phalangeal bone mineral mass because the effects of soft tissue and matrix are substantially removed by the computation. The computer calculates the bone mineral (area density) by taking the ratio of mass to area from the densitometer's optical density readings and the bone width values (2). The mineral mass is expressed in computer units rather than in grams. The entire process is repeated for the second radiograph in order to check the results from the first analysis. The two films are taken at deliberately different kilovoltages and usually at a different milliamperage (ma) exposure in order to determine if the wedge scan and computer calculations compensate adequately for differences in radiologic technique and film processing procedures (7). The analyses are rejected if between-film disagreements greater than $\pm$ 3 percent (from their mean) can not be explained by a known system or operator error on one of the films. Otherwise, the average mineral density and bone area obtained from both radiographs are used for evaluating the patient.

The phalanges are a mixture of compact and cancellous bone, and RA does not reveal the distribution of mineral within the bone. Using RA, the bone mineral measured reflects the total integrated mineral (cortical and trabecular) in the path of the photons. Similar to the process of single photon absorptiometry (SPA), RA is limited to

measurements of appendicular bone because tissue composition surrounding the bone has to be minimal. Corrections cannot be made by this instrument for bones embedded in thick soft tissue (3).

Although the radius and other appendicular bones may be studied, the use of RA has been confined to the phalanges. Currently, the cost of analysis of a pair of films is approximately $65. A comparison of RA costs with those of other techniques for measuring bone mineral can be found in the costs section of the Office of Health Technology Assessment (OHTA) assessment for dual photon absorptiometry (DPA) (8).

Radiation exposure is always a concern with any procedure utilizing radiation sources. While RA is a noninvasive technique, it does involve patient exposure to radiation. According to the position paper on radiologic methods to evaluate BMC from the Health and Public Policy Committee of the American College of Physicians, RA involves minimal radiation exposure (up to 100 mrad), with negligible bone marrow or gonadal radiation (6). According to Chesnut, less than 10 mrem of radiation exposure are associated with the RA technique (9).

The physiologic information provided by measurements of BMC have been under extensive investigation during the past 20 years. Bone mass measurements have been a valuable research tool for clinical investigations attempting to elucidate the pathogenesis of metabolic bone diseases. Investigators have sought to determine the clinical significance of bone loss with aging and bone disease and its relationship to an increasing risk of fractures among the elderly. This growing interest in a better understanding of the nature and degree of changes in BMC with age, osteoporosis, and with metabolic bone disease in general, has prompted the development of nonivasive measurement techniques for assessing BMC (3). A variety of such techniques in addition to RA are presently available. They include: radiogrammetry, SPA, computed tomography (CT), and DPA.

Bone mineral measurements using RA have been utilized mostly in the management of patients with chronic renal failure and for osteoporosis detection in women (7). This report will reassess the effectiveness of RA bone mineral measurements on the clinical outcome of patients being evaluated and treated for osteopenic bone diseases. This reassessment seeks to ascertain the place of bone mineral evaluation by RA in the overall scheme of prevention, diagnosis and treatment. Similar reports have been published on SPA and DPA. The other noninvasive measurement techniques for BMD will be assessed in separate reports.

BACKGROUND

Osteoporosis is a major public health problem and renal osteodystrophy is a major clinical complication experienced by patients on chronic dialysis. The National Institutes of Health Consensus Development Conference on Osteoporosis held on April 2-4, 1984, reported that osteoporosis may affect between 15 and 20 million Americans (10).
More than one million fractures attributable to osteoporosis occur annually in individuals over the age of 45. In women over 60, 25 percent have documented vertebral fractures by age 75. These fractures may develop during routine activities, such as bending, lifting, or raising from a chair or bed (10). While compression fractures (collapsed fractures) of the vertebrae can produce severe pain, most cases are painless. The amount of pain and disability attributable to vertebral fractures is unknown. According to the American College of Obstetricians and Gynecologists, after age 45 there is a marked increase in the incidence of distal forearm fractures (11). By age 60, there are 10 times more forearm fractures in women than in men of comparable age. These fractures limit the use of the extremity for 4-8 weeks, with long-term disability uncommon. While osteoporosis predisposes to fractures of various bones, hip fractures are the most serious in terms of disability, mortality, and aggregate cost. In the United

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States, it is estimated that more than 200,000 hip fractures occur in elderly women each year with 80 percent found to be related to pre-existing osteoporosis (11). The affected population tends to be advanced in age, with the sex distribution less skewed toward females than is the case for vertebral fractures. Acute complications such as depression and mechanical failure of the surgical procedure are common (10). Most patients fail to recover normal activity. Hip fractures lead to fatalities in 12 to 20 percent of cases and precipitate long-term nursing home care for half of those who survive (12, 13). Thus hip fractures pose a significant economic as well as a medical burden.

The economic burden of all age-related fractures is great because of the large number of people involved and the expensive and protracted care that is often required. About one-fourth of all patients with limb fractures require hospitalization and the mean hospital stay increases from 13.6 days among those age 25-44, to 32.6 days among those older than age 65. Fractures of the proximal femur account for more than half of all days of hospitalization for limb fractures. In the United States, the annual cost of the acute care alone for fractures of the proximal femur has been estimated to exceed one billion dollars (14); the annual direct and indirect costs of osteoporosis, including hip fractures, are estimated to be between $3.5 billion and $6.1 billion (10,13). As a result of the considerable morbidity, mortality, and expenditures associated with this disease, there is growing interest in research regarding its prevention, diagnosis, and treatment. The pathogenesis of osteoporosis, its prevention, and its management has had extensive review. A summary of that information can be found in the osteoporosis section of the OHTA assessment on DPA (8). Additional information can also be obtained from the numerous references cited in that report.

Renal osteodystrophy is a generic term that describes a number of distinct skeletal abnormalities that are present in the majority of patients with advanced renal failure (15). Hyperparathyroidism, disorders of vitamin D metabolism, chronic metabolic acidosis, and excessive fecal losses of calcium all contribute to the occurrence of bone

diseases in uremia (16). The longer life is preserved, particularly by treatment with hemodialysis, the greater probability of developing osteodystrophy. Although clinical symptoms of bone disease are uncommon, occurring in less than 10 percent of patients with advanced renal failure, radiological and histological abnormalities are observed in about 35 and 90 percent, respectively (16).

Renal osteodystrophy is a complex disturbance of bone comprising varying degrees of osteitis fibrosa cystica, osteomalacia, osteosclerosis, and generalized osteopenia. The main components of renal osteodystrophy are osteitis fibrosa and osteomalacia. A lesser role is played by osteosclerosis and osteoporosis. The etiology is not completely understood, but impaired vitamin D metabolism, secondary hyperparathyroidism, diminished gastrointestinal absorption of calcium, and occasional aluminum toxicity all may play a role (17).

Most of the symptoms related to renal osteodystrophy appear only when renal failure is advanced (15). Manifestations of osteodystrophy include bone pain and fractures. Accompanying abnormalities include muscle weakness, soft tissue and vascular calcification and pruritus (17). Certain biochemical alterations may appear early in the course of renal insufficiency. Knowledge of the presence of these alterations may help the physician introduce treatment early in the course of renal failure and aid in the prevention of severe complications in bone and mineral metabolism (15). One of the early changes in patients with renal insufficiency is the presence of elevated levels of circulating immunoreactive parathyroid hormone (i-PTH). Parathyroid hormone increases the net release of calcium from bone into extracellular fluid. In this defense of calcium homeostasis, the hormone influences the differentiation and activities of bone cells (18).

A rise in the serum phosphate concentration is also observed when the glomerular filtration rate (GFR) below approximately 25 percent of normal. Because calcium deposition in bone is critically dependent upon the availability of phosphate, retention of

phosphate in plasma will facilitate calcium entry into the bone. This contributes to hypocalcemia and to the elevations in plasma PTH levels seen in chronic renal failure (16). Management of patients with renal osteodystrophy includes measuring and/or controlling serum levels of calcium, phosphate, and bicarbonate (15,19). These tests are presently included in the protocol of laboratory tests for the management of end-stage renal disease dialysis patients. Radioimmunoassays for monitoring the level of circulating i-PTH has also been recommended (15,18). Moreover, it has been recommended that measures for the control of the abnormal mineral metabolism of renal disease begin early in the course of the disease, when the GFR is 30-40 mL/ min (15). According to Slatopolsky and Kokko, when such treatment is instituted early in chronic renal failure, signs and symptoms of renal osteodystrophy and parathyroid gland hypertrophy may be prevented (15,19).

Conversely, Muirhead and associates have found the management of dialysis osteopenia difficult (20). They reported that measures aimed at treatment of associated metabolic bone disease, such as administration of calcium supplements, vitamin D, 1 hydroxyvitamin D_3, or parathyroidectomy, have no consistent effect on skeletal mineral content over the long term. At best, long-term treatment can be expected to slow the rate at which skeletal demineralization progresses rather than producing a sustained increase in BMC (20).

For the past 12 years, investigators have used RA to assess the BMC of the appendicular skeleton in "normal" individuals and in patients with renal osteodystrophy and osteoporosis. Few studies, however, have been conducted to investigate whether appendicular (phalangeal) bone mineral measurements could predictably separate normal women from women with vertebral compression fractures or femoral neck fractures. Investigators have also used RA measurements to identify patients ostensibly at risk for future fractures. This report examines these and other studies as well as other evidence that pertains to the safety and clinical effectiveness of this technique.

RATIONALE

The rationale for bone mineral measurements is based on the demonstration that the strength or resistance of a bone to fracture is closely related to the amount of bony tissue or the mass of the mineral present in the bone. Proponents argue that since the tensile (breaking) strength of bone is related to its mineral content, measurements of bone mineral should be a more accurate method of determining fracture risk. Proponents of RA believe that the ability to assess the direction and degree of changes in BMC in the phalanges facilitates the diagnosis and management of metabolic bone diseases, such as renal osteodystrophy and osteoporosis. Proponents also argue that these measurements could prove useful as clinical guides to therapy in assessing the therapeutic responses of patients with osteopenia. They argue that RA is low in cost and radiation exposure, uses only the x-ray equipment readily available at every hospital, and requires no special training of hospital personnel.

REVIEW OF AVAILABLE INFORMATION

Accuracy and Precision

Accuracy defines the degree to which a measurement, or an estimate based on measurements, represents the true value of the attribute that is being measured. In this case it refers to how well the measurement reflects actual mineral content. It is expressed as a coefficient of variation (or error of estimate) of the difference between actual and measured. In the determination of osteopenia, accuracy in the measurement of bone mass by RA is of great importance.

Whereas accuracy refers to the correctness with which a certain reading represents the true value, precision refers to the width of the range of indicated values. In monitoring changes in bone mass, RA bone mineral measurements have to be sufficiently precise (reproducible) to provide a correct estimate of these changes. Precision is important if the goal is to detect small changes in bone mass. The coefficient of variation (cv), expressed in percent, describes the precision or reproducibility of a given measurement.

Technical problems affecting precision and accuracy generally associated with photodensitometric methods include scattered radiation from the broad x-ray beam, a variable energy spectrum leading to uncertainties in the effective absorption coefficients of bone and soft tissue, and beam hardening of the energy spectrum in passing through soft tissue (21). Colbert and Bachtell have indicated that for small bones with thin flesh cover, such as the phalanges, the background optical density value is assumed to adequately correct for scatter if it is uniformly distributed over the bone image. In addition, the x-ray beam can be considered to have a single "effective" photon energy and there is no beam hardening (2). To minimize or prevent measurement errors that would result from different x-ray machines, kilovoltage and exposure settings, film types and film processing, Colbert and Bachtell derive correction terms from pixel data taken from a scan of the reference wedge image. According to the investigators, the wedge image is scanned to provide data for the absorption coefficient of the aluminum alloy which accounts for differences in x-ray spectrum due to tube characteristics, kilovoltage, waveform, and prefiltration. The scanning also provides the background optical density due to film base, fog, and scatter, which are a function of exposure, measured in milliampere-seconds (mA-s), and film processing procedures. Once these two values are obtained, a computer calculates the terms that automatically correct for the differences described above (2).

To minimize measurement errors due to spectrum shifts, uneven scatter distribution, incorrect film background density determinations, overexposure, underexposure, uneven film development, densitometer errors and nonlinearity, soft-tissue covering, and variations in reference wedge composition, Colbert and Bachtell recommend repeat readings averaging the results (2). They believe that system errors such as edge detection errors, computational errors, and scanner malfunction will be reduced because the mineral density data are read from three complete phalangeal bones from two separate radiographs and compared before they are averaged (2).

The instrumental accuracy of RA was studied by Colbert and co-workers in 1970 (21). Eighty-five excised bones and an aluminum reference wedge were measured under water to simulate a constant thickness of soft tissue surrounding the limb, and the mass of the ashed bone sections were compared with RA measurements. Ash weights of the bone sections ranged from approximately 0.4-2.0 g. According to the authors, the error in predicting ash weight using RA was 6 percent under these test conditions that included exposing all bones on a single radiograph under standard conditions.

To evaluate RA reliability with varying exposures, radiographs of the bone sections were made at 50 and 70 mA-s Although the measurements of the same 85 bone sections from films at 50 and 70 mA-s exposure gave a high correlation (r=0.990), the standard error of estimating indicated a prediction error of 4.4 percent (21). By averaging repeated measurements the prediction error from the different films was reduced to less than 4 percent. Colbert suggested that the use of the uniform bolus of tissue-equivalent material (water) surrounding the bone and the correction for background density of the radiograph were responsible for the increased accuracy of this technique over other photodensitometric techniques (21).

In a similar study of RA accuracy, Colbert and Barzel compared excised rat bone mineral measurements by RA with mineral content (as weight) determined gravimetrically (22). Forty-two excised rat bones and an aluminum reference wedge

were measured under several centimeters of water and the mass of the ashed bone sections were compared with RA measurements. Regression analyses showed that RA measurements again predicted ash weights within ± 6 percent.

Because the measurement error introduced by soft tissue in photodensitometric techniques has been recognized by many investigators, the procedure has usually required water immersion of the body part and wedge for correction of the effect of soft tissues (21,23). The addition of water compensates for variations in tissue thickness and provides a uniform tissue equivalent thickness (24). It also provides exposure conditions of the calibration wedge similar to those for the bone. In the 1970 and 1972 studies by Colbert and co-workers the procedure included the immersion of the body part and wedge in water.

However, in 1979, Colbert and Bachtell reported that x-rays of small bones with minimal soft-tissue cover (phalanges) do not require immersion in water (1). They found that the linear absorption coefficient of the wedge (in air) varies with photon energy in nearly the same manner as the wedge x-rayed in water and could be used in its place by applying a constant adjustment factor (1). According to Wahner and colleagues, the only photodensitometry method currently acceptable immerses the hand in water for constant soft-tissue thickness, and uses a microdensitometer and computer (3). Mazess and Cameron in agreement with Wahner and colleagues, believes that the extent of air measurement deviations (from water) depends on the effective energy of the x-ray beam (spectrum) and therefore can not be corrected by a constant multiplier (25). This issue remains controversial.

In 1983, Bachtell compared RA measured mineral weight with the ash weight of 14 phalangeal cadaver bones (26). Fourteen phalangeal cadaver bones were defleshed and radiographed in groups of two or three bones at 50 and 60 kVp. Bachtell found that the

ash weights regressed linearily against the radiological weights to give a prediction error of 3.7 percent and a correlation coefficient of 0.997. The cadaver bones and aluminum alloy reference wedge were radiographed under a thin water cover.

Results from a study of bone mass in 50 postmenopausal osteoporotic women at the University of Washington were reported by Chesnut at the National Institutes of Health (NIH) Consensus Development Conference on Osteoporosis (9). Using RA measurements of the phalanges, he found a precision of 2-3 percent. Similar levels of precision (1-4 percent) have been reported in the position paper on radiologic methods to evaluate bone mineral content from the Health and Public Policy Committee of the American College of Physicians (6). The position paper also reported 6 percent reliability (accuracy) for the RA technique.

Recent information from Bachtell and Colbert indicates that the precision of the RA technique is between 2 and 4 percent (27,28). In one cited study, BMD was determined from radiographs of a phantom hand taken over a 3-year period at eight different hospitals using nine different x-ray machines. The precision was 3.7 percent when the selection criteria of radiographs included those taken outside recommended specifications for kilovoltages and optical density (27). Allowing for changes in the system and deletion of defective radiographs and radiographs recorded outside of the specifications, the precision was improved to 2.5-3.0 percent (27,28). However, radiographs taken in violation of the recommended specifications are frequently included in BMD determinations.

In a similar study to determine the precision of the RA technique, BMD was determined from radiographs of the same left hand taken over a 10-year period at 10 different hospitals using nine different film types. The precision, depending upon the selection criteria of the radiographs, was between 2.9 and 4.1 percent (29).

Clinical Applications

In 1971, Goldsmith and co-workers used several techniques, including RA, to estimate BMC in normal and osteoporotic women (30). Using BMD values based on RA measurements of the middle phalanx of the ring and index fingers the investigators were unable to clearly separate normal women from women with moderate or severe osteoporosis.

In 1977, Colbert and colleagues reported using RA for BMD determinations in patients with chronic renal failure (31). In preliminary findings, 160 patients with chronic renal failure had average BMD values lower than reference means derived from age- and sex-matched control subjects. They believed this indicated a tendency toward osteopenia or osteodystrophy. Although the authors were reporting patient progress for less than 1 year, they recommended that patients should be followed for 3 years or more to ascertain reliable trends (31).

At the Fourth International Conference on Bone Measurement, Zanzi and co-workers presented data from a study that determined the relationship of total body calcium (TBCa), measured by total body neutron activation analysis, with BMC of the phalanges, measured by RA, and BMC of the radius measured by SPA (32). These techniques were applied to two groups of subjects: In the first group there were 16 patients (14 female, 2 male) with primary osteoporosis; and in the second group, 14 healthy male marathon runners. The investigators found a correlation between measurements of TBCa and BMC at the phalanges in the osteoporotic female population (r=0.66). The correlation between TBCa and BMC of the phalanges in the marathon runners was less (r=0.57). However, the investigators also reported that the scatter of the data could result in an error in measurement prediction of $\pm$ 7-14 percent (32).

According to Zanzi and associates, the level of correlation and standard errors of estimate attained precludes a reliable prediction of bone mineral from the phalanges to the total body in a particular individual. Used alone, TBCa data do not give a complete

separation of individual osteoporotic patients and normal subjects. Zanzi's group did suggest that RA measurements of the phalanges are adequate for use in epidemiological surveys of the bone mass of populations, or in serial evaluations of bone mass, particularly cortical bone (32).

In a continuation of the work by Colbert (31), Chester and associates studied the effectiveness of RA to assess the extent and the therapy of renal osteodystrophy (33). They compared visual review of hand radiographs with RA determinations in 179 patients with chronic renal failure. Although the investigators demonstrated some agreement between RA determinations and visual review of hand radiographs when changes were noted by the radiologist, the agreement with RA was at best moderate; they concluded that RA may be a more sensitive method of appraising renal osteodystrophy than visual reviews of hand radiographs. Chester and associates also suggested that RA determinations may indicate changes in the clinical features of renal osteodystrophy not suggested by serum calcium, phosporus, or alkaline phosphatase. This conclusion was based on a study of only eight patients with bone gain whose serum calcium, phosphorus, and alkaline phosphatase were no different (statistically) when compared to eight patients who had lost bone at an accelerated rate (33).

At the 1981 Jerusalem International Symposium on Osteoporosis, Bachtell and Colbert (34) presented data on the RA technique that updated the 1971 study by Goldsmith and associates (30). Because the mineral estimates made by the earlier RA technique did not agree with the visual osteoporosis classifications, the investigators improved the system and rescanned 49 usable radiographs from the original experiment. With the improved RA determinations, the authors found good agreement with the visual classifications. Also, the mean BMD of the normal group was significantly greater than that of the moderate plus severe osteoporotic group. However, because of the sizable overlap in BMD among the groups, bone mineral measurements of the phalanges may be unsatisfactory for evaluation of the extent of osteoporosis in an individual (34).

In a recent study, Colbert and associates used RA to determine the effect of continuous ambulatory peritoneal dialysis (CAPD) on phalangeal BMD (35). Over a 2-year period they measured and compared the BMD average rate of change of patients from one group on CAPD (N=32) and five groups on hemodialysis (N=323) with the BMD normal rate of change due to aging. Colbert and associates found that as a group, the 32 CAPD patients who had normal BMD means and distributions at baseline lost BMD, on the average, at the same rate as the controls. He also found that for four of the five patient groups on hemodialysis, BMD declined at rates significantly greater than normal. The groups were not matched for age, sex, or for any other parameters (35). After an additional year of followup, Colbert and associates confirmed their earlier findings that, on the average, the CAPD patients lose BMD at a rate not significantly different from the normal rate related to aging (36).

At the 1984 Copenhagen International Symposium on Osteoporosis, Ott and colleagues reported preliminary results of a study that compared several techniques, including RA, for the measurement of bone mass at different sites in the same group of patients (37). They sought to determine whether a measurement of bone mass at one site could predict bone mass at a second site in a population of women with postmenopausal osteoporosis. The study group consisted of 66 Caucasian women, ranging in age from 51 to 80 years, who had evidence of vertebral compression fractures. Significant but modest correlations between the various bone measurements were reported. Although measurements of TBCa and BMD at the phalanges had a significant correlation of 0.73 ($p < .001$), the investigators found that the standard error in estimating the TBCa from the other measurements was 10-15 percent. The correlation between RA measurements of the phalanges and DPA measurements of the spine was 0.56 ($p < .001$). However, the standard error in estimating the BMD at the spine from the RA phalangeal measurements was not given.

According to Ott and associates, discrepancies in measurements may be caused, in part, by the different ratios between cortical and trabecular bone at the different sites measured (37). Ott suggested that if a patient had a disproportionate loss of cortical or trabecular bone, then measurements at the spine would not correlate with those of the total body or peripheral sites.

At the same symposium, Bachtell and Colbert presented preliminary findings of a longitudinal study that used RA phalangeal mineral measurements to identify patients with a rapid loss of bone mineral (38). The investigators recorded bone mineral at 6-month intervals in 146 female subjects, mostly in their 60s, for 1 1/2-3 years. Comparing the decline of phalangeal mineral density in the 146 subjects with the average annual decline of phalangeal mineral density (1.2 percent) in a normal population of similar age, the investigators determined that 37 subjects (25 percent) of the test population had rapid loss of bone mineral (38). However, these measurements have uncertain value for predicting future rates of bone loss or assessing risk for fractures. They also ignore the fact that an accelerated bone loss has been reported in normal women following menopause.

In 1984, Bachtell noted that other investigators had observed statistically significant correlations between RA measurements of the phalanges and SPA measurements of the radius in 61 ambulatory postmenopausal osteoporotic females (39). Bachtell also compared the RA phalangeal bone mineral measurements of osteoporotic women in this group and a second similar group (N=63) with the the RA phalangeal bone mineral measurements of 377 normal females (40). An osteoporosis risk threshold was arbitrarily chosen to be one standard deviation (16 percent) below the mean mineral volume density of young normal adult women (20-50 years of age). This resulted in 80 - 90 percent of the osteoporotic females having BMD levels that fell below this value. However, values for the women in both osteoporotic groups clustered about peer norms with no significant difference between the normal mean and the subject mean. Bachtell

concluded that the osteoporosis risk threshold was an excellent discriminator of postmenopausal women who have a high risk of vertebral compression fractures. This conclusion was reached without the benefit of clinical information regarding the extent of vertebral compression fractures in the normal control group. Moreover, after age 60 almost all the women in the normal control population had values below the osteoporosis risk threshold (40).

According to Bachtell, in lieu of a prospective study to determine how well postmenopausal women who will eventually experience bone fracture can be separated from those who will not exeperience fracture, one determines how well osteoporotic women can be screened from nonosteoporotic women. In order to evaluate the screening efficacy of RA measurements, Bachtell plotted the number of true-positive results (osteoporotic women who fall below the screening threshold) from groups of confirmed osteoporotics women versus the number of false-positive results (nonosteoporotic women who fall below the threshold) from the reference females between the ages of 20 and 50. Plots of true-positive versus false-positive results are called receiver operating characteristic (ROC) curves. The higher the percentage of true-positive and the lower the percentage of false-positive results, the better the screening system (41).

Choosing a phalangeal mineral density threshold of 100 units, Bachtell was able to obtain percentages of women with true-positive results that ranged from 82-96. Using the mineral density values of the reference females between age 20 and 50, he was able to obtain a false-positive percentage of 11.5. This study demonstrated high sensitivity and high specificity of RA measurements in screening females with vertebral fracture from midlife (20-50 years) normal women. However, Bachtell showed in an earlier report that after age 60 almost all women in the normal reference population were below the osteoporosis risk threshold. This indicated that if data from a nonosteoporotic group similar in age to the osteoporotic groups were plotted, the specificity of the screening test would be low (40).

Monroe used RA measurements to screen 355 postmenopausal women for estrogen replacement therapy for prevention of postmenopausal osteoporosis (42). In 1986, he reported to the Ohio Academy of Family Physicians that a threshold of one standard deviation below the mean bone density value of normal women, 20-50 years old identified 145 (41 percent) of the women "at risk" and in need of estrogen management. Although this risk threshold is arbitrarily designated and not based on a prospective study of fracture incidence, most of the 145 women were recommended for estrogen therapy, which was accepted by 95 of them (42).

In 1986, Rosenthal and co-workers reported on a retrospective study that compared the ability of several bone measurement techniques, including quantitative computed tomography (QCT) and RA, to discriminate between patients with and without fractures (43). Selected for the study were 102 consecutive patients (74 females and 28 males) clinically suspected of having abnormally low skeletal mass; 74 of the 102 patients were age 51 or older. When patients were divided into groups with and without lumbar vertebral compression fractures, QCT provided the best separation between the two groups, ($p < .001$), with relatively little overlap. Although Rosenthal found the mean values for RA to be significantly different between the two groups, there was considerable overlap. The RA measurements of phalangeal trabecular bone were only weakly correlated with QCT measurements of spinal trabecular bone. The RA measurements of the composite mass (cortical and trabecular) of the phalanges were approximately equally correlated with the QCT measurements of spinal trabecular bone (43).

Rosenthal found that RA measurements provided the best correlation with long bone fractures (such as hip and radius); however, prediction of peripheral fractures was considered unsatisfactory by all methods. He suggested that these results may indicate that trauma is more important in the causation of extremity fractures than of vertebral compressions, a feature that cannot be predicted by any measurement (43). According to

Rosenthal, any widely useful technique for measuring bone mineral must help predict the risk of fractures in the general public. Therefore, while this retrospective study showed that QCT measurements of the spine could reasonably discriminate fracture and non-fracture patients, a prospective study is necessary to determine if those same measurements can accurately predict fracture incidence (43).

Most recently, Colbert and associates reported completing a brief study of RA-BMD measurements in 14 end-stage renal disease (ESRD) patients who subsequently underwent parathyroidectomies (44). The study was performed to determine the efficacy of RA-BMD measurements of the phalanges as an indication for surgical intervention and surgical success. This was to be determined by comparing changes in RA-BMD measurements with corresponding serum chemistries. In most instances of surgical success, as judged by serum chemistries, there was a corresponding improvement in BMD. However, Colbert acknowledged the small sample size and the need for more complete serum chemistry data and for longer observation periods in more patients. The study failed to support the conclusion of the authors that RA monitoring of phalangeal BMD is of help in deciding when to perform a parathyroidectomy on an ESRD patient. It has not been made clear by the investigators how RA bone mineral measurements would change the management based on the serum chemistries of these ESRD patients (44).

Occasionally there is a patient with severe secondary hyperparathyroidism and evidence of hypercalcemia in whom parathyroid surgery may be required to reduce excessive amounts of circulating parathyroid hormone (PTH). Close monitoring of PTH, calcium, and phosphate is essential in the management of these patients. Monitoring BMD by RA may also be of help in judging the success of the surgery and should be studied further.

DISCUSSION

The measurement of bone mass is an important tool in the study of metabolic bone diseases, particularly osteoporosis. Current interest is centered on the recent advances in bone mineral measurement techniques including RA. This interest in RA is based on the belief that bone mineral measurements of the phalanges facilitates the diagnosis and management of metabolic bone diseases, such as renal osteodystrophy and osteoporosis. Presently, RA has utility in clinical research in studying the natural history of primary osteoporosis and renal osteodystrophy in large populations and in studies evaluating preventive and therapeutic regimens. However, while RA is capable of measuring bone mineral and has advanced our knowledge of bone disease in general, its role in the management of the individual patient is uncertain.

It would be advantageous to be able to prospectively identify those women who are at risk for developing osteoporotic fractures, in order to direct treatment to those at greatest risk. As a screening test for osteoporosis in perimenopausal women, this application of RA bone mineral measurements is suggested to have potential utility. Once established as a screening tool it could be used in the strategy for treating afflicted individuals or preventing osteoporosis. Although the technology to noninvasively measure bone mineral with RA is currently available, the ability of such measurements to identify those individuals who will subsequently experience bone fracture has not yet been shown.

Presently, there has been no prospective study demonstrating that the noninvasive measurement of bone mass by RA can identify patients who will suffer fractures. In their 1984 review of the various noninvasive methods for bone mineral measurements, Wahner and colleagues concluded that there was no optimal technique available for mass screening for early osteoporosis (45). The American College of Physicians' Health and Public Policy Committee recently reviewed various radiologic methods for measuring BMD, including RA, but made no recommendation about the use of these tests in routine

screening for osteoporosis (6). In order to predict a female individuals' fracture risk, it would be necessary to study large population cohorts of women from various age groups and relate their specific bone measurements to prospective fracture incidence data collected over a sufficient period of time. Using fracture incidence data, the risk ratio would provide an estimate of risk. This type of study would enable investigators to determine whether it was possible to predict the risk of fracture from the initial bone density measurements. A patient's bone mass measured before or at menopause may indicate whether she has low or high bone mass for her age. It will not necessarily indicate whether she will fall into the high-risk group 10-15 years later, when most fractures occur. The contribution of bone mass at maturity versus subsequent rates of loss is still largely unknown. Moreover, there exists a controversy regarding the selection of a screening site. While many investigators consider BMD measurements of the actual fracture site (spine and hip) paramount, others argue that fracture risk prediction and screening can be accomplished by appendicular BMD measurements. According to Riggs and Melton, appendicular measurements would be of little value for predicting the risk of fracture in the spine or hip (13).

Initially, investigators used RA bone mineral measurements in attempts to find a specific level of bone density that clearly distinguished patients with vertebral osteoporosis. Those studies, including the work of Bachtell and Colbert and more recently Rosenthal and co-workers, have been largely unsuccessful in determining such a level (34,43). When patients were divided into groups with and without lumbar vertebral compression fractures, Rosenthal found that the mean values for RA differed significantly between the two groups, but there was considerable overlap (43). Other investigtors, such as Riggs and colleagues, who also were unable to clearly distinguish patients with vertebral osteoporosis, consistently found less trabecular bone, on average, in women with vertebral fractures (46). From their study of risk factors for injury after a fall, Melton and Riggs concluded that a reduction in spinal bone mass is the primary

determinant of who will suffer vertebral fractures (47). According to Cummings and associates, measurement of vertebral BMD may be a useful way of identifying women at greatest risk for vertebral fractures (48).

With regard to peripheral fractures (hip and radius), Rosenthal considered separation of patients with peripheral fractures unsatisfactory by all methods of measuring bone mineral, including RA. He suggested that trauma may be more important in causation of extremity fractures than of vertebral compressions, a feature that can not be predicted by any measurement (43). The failure of other bone density measurement techniques to clearly distinguish fracture patients from age-matched controls has prompted other investigators to concur that in addition to low bone mass, which is nearly universal among the very elderly, other factors are important in predicting who will experience a hip, or Colles' fracture.

Other studies of RA investigated the correlation between bone density measurements of the phalanges and TBCa measured by total body neutron activation analysis (32,37). The studies by Zanzi and co-workers and Ott and colleagues indicated that a correlation between measurements at two sites (phalanges and total body) does not necessarily mean that one measurement may accurately predict the other (32,37). Even significantly correlated measurements with a large standard error (scatter) precludes a reliable prediction of bone mineral at one site based on measurements at another site in a particular individual.

In two studies, RA measurements of phanageal BMD were, at best, only moderately correlated with spinal BMD measurements (37,43). According to Ott and associates, if a patient has a disproportionate loss of cortical or trabecular bone, measurements at the spine would not correlate with those of the total body or peripheral sites.

In 1984, when Bachtell compared the RA phalangeal bone mineral measurements of two groups of osteoporotic women with a large group of normal females, he found that the measurements in both osteoporotic groups clustered about peer norms with no

significant difference between the normal mean and the subject mean (40). However, by arbitrarily choosing a phalangeal mineral density of 100 units and comparing the BMD values of these osteoporotic postmenopausal women with the BMD values of normal females 20-50 years of age, he was able to distinguish patients with osteoporosis. After age 60 almost all the women in the normal control population were below the osteoporosis risk threshold (40).

If phalangeal bone mass in the elderly does not differ in patients with and without fractures, these measurements would be of little or no value in predicting which elderly patients are likely to incur a fracture. Measurements of phalangeal bone mass may not be a reliable way to identify those at greatest risk for fracture. According to Bachtell, almost all the women 60 years and older in the normal reference population are at risk because their BMD values are below the phalangeal mineral density threshold of 100 units (40). That being the case, treatment methods could be undertaken without the use of individual RA bone mineral measurements. It is not certain what value RA measurements of phalangeal bone will have in identifying women at greatest risk for fracture. This application of the RA method needs further clinical investigation before it is advocated for widespread use or before it is employed as a basis for recommending specific types of preventive therapy.

Another clinical application proposed for the RA technique has been the use of RA measurements to monitor the rates of bone loss and the effectiveness of treatment. This could apply to the treatment of individuals with established osteoporosis and also to those receiving preventive regimens. Because rates of bone loss are relatively small compared with the reproducibility of the measurement, current methods for measuring bone mass, including RA, may not be sufficiently precise for clinical decisions in an individual (49,50). As stated earlier RA is reported to have a precision of 2-4 percent, and the average rate of appendicular bone loss in women is 1 percent per year in the decade after, and less before, natural menopause. According to Cummings and Black, for

women, a measurement of the rate of bone loss based on two measurements of bone mass over a period of time leaves considerable uncertainty about the rate of loss. A bone loss of 3 percent measured by a technique with a 2-percent reproducibility (RA) leaves a considerable uncertainty about the actual rate of loss (the 90 percent confidence interval for that change in bone mass varies from a 1.7 percent gain to a 7.7 percent loss) (49). Unless multiple measurements are made, a woman must lose a substantial amount of bone during the time between measurements before a physician can conclude that she is losing bone more rapidly than normal (49). However, even these additional measurements have uncertain value for predicting future rates of bone loss or assessing risk for fractures and would substantially increase the expense of management. Riggs and Melton believe that measurements every 6 months over 2-3 years may be required to estimate individual rates of bone loss (13). According to Ott, until such time as more sophisticated methods of improving the reproducibility are developed, techniques for measuring bone mineral, such as RA will be valuable in studying large groups of patients, but will not be helpful in individuals (50).

Still uncertain, however, is the suitability of the phalangeal bone site as the appropriate location to determine rates of bone loss or the effectiveness of treatment. Even if the RA technique is shown to be adequate for determining rates of bone loss or gain by sequential measurements, there would be uncertainty as to whether the results would reliably reflect bone loss or gain in the spine or hip. Moreover, according to Lindsay and mentioned at the recent NIH Workshop on Osteoporosis, there is no current evidence that serial bone mass measurments need to be performed in patients receiving adequate estrogen therapy, since studies indicate that more than 90 percent of these patients will be protected against bone loss (51).

Some investigators have reported using RA measurements of phalangeal BMD to assess the extent and the therapy of renal osteodystrophy (31,33). Colbert and associates have investigated the efficacy of RA-BMD measurements of the phalanges as an

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indication for parathyroid surgical intervention and success (44). Because biochemical alterations may appear early in the course of renal insufficiency, the prevention and management of renal osteodystrophy includes the control and monitoring of serum calcium and phosphate concentrations (15).

Secondary hyperparathyroidism with renal osteodystrophy is a frequent if not universal complication of chronic hemodialysis (52). Phosphate retention, developing early in renal compromise, contributes to most of the components of renal osteodystrophy (17). The initial stimulus of secondary hyperparathyroidism is believed to be a chronic reduction of ionized calcium in the extracellular fluid due to renal retention of phosphate (53). Because calcium deposition in bone is critically dependent upon the availability of phosphate, retention of phosphate in plasma facilitates calcium entry into bone and contributes to the hypocalcemia observed in chronic renal failure.

Secondary hyperparathyroidism is a state of compensatory hypersecretion of PTH and may occur where there is a tendency toward hypocalcemia. Excessive levels of PTH accounts for many of the bone changes of renal osteodystrophy, including osteitis fibrosa and osteosclerosis (54). Importantly, one of the early changes in patients with renal insufficiency is the presence of elevated levels of circulating i-PTH. Knowledge of the presence of these and other biochemical alterations should help the clinician to introduce treatment early in cases of renal failure and aid in the prevention of severe complications in bone and mineral metabolism (15). According to Clark, maintaining relatively normal serum concentrations of calcium and phosphorus during hemodialysis has dramatically decreased incidence of bone disease (52). Drach recommends obtaining a fasting serum calcium level with a simultaneous measurement of serum PTH (55).

A review of the literature indicates that the information regarding the levels of calcium, phosphate, i-PTH, and other chemical entities obtained from clinical chemistry testing, is sufficient for the management of renal osteodystrophy. The need or

appropriateness for RA-BMD measurements of the phalanges in the management of renal osteodystrophy has not been established in the studies presented.

Advice and comments concerning the safety and clinical effectiveness of RA has been sought from groups and organizations within and outside of the Federal government. An announcement of this assessment appeared in the Federal Register notice of October 26, 1984 (56). On June 20, 1985, in testimony before the Subcommittee on Aging of the Committee on Labor and Human Resources, United States Senate, representatives of NIH, through the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases (NIADDK), stated that it was a research imperative to develop better methods for measuring bone density (57). In addition to diagnosis, these methods should enable early identification of bones most vulnerable to fracture and provide a measure by which to evaluate the effectiveness of new therapies. According to NIADDK, while several noninvasive methods for measuring bone density have been developed, at present no existing techniques can adequately discriminate, early in the disease process, between normal and osteoporotic individuals (57). The NIADDK recommended long-term clinical trials of various specific patient populations, in numbers large enough to provide valid and reliable estimates of risk, and to determine the optimal regimens to prevent bone loss and fracture.

At that same hearing on osteoporosis, the National Institute on Aging (NIA) stated that there is a need for better ways of identifying persons at high risk for fracture, since those individuals could be expected to benefit most from treatment (12). Because it is still unclear which persons would benefit from which treatment, and at what dosages and schedules, additional research and clinical trials are needed to develop the current state of knowledge regarding prevention and treatment of osteoporosis for specific individuals or groups. The American College of Obstetricians and Gynecologists, in their statement before the Subcommittee on Aging, indicated that presently there are no tests to identify

which women are at risk for developing osteoporosis (11). The College recommended, however, that the physician determine bone loss by absorptiometry in their diagnosis of osteoporosis.

The NIH Consensus Development Conference on Osteoporosis was held on April 2-4, 1984 (10), approximately 14 months prior to the Senate Hearing on Osteoporosis. At that conference, data were presented that showed that none of the noninvasive techniques for measuring bone mass were able to significantly discriminate between normal and osteoporotic individuals. None of the techniques for currently quantitating bone mass can definitely predict the individual at significant risk for fracture. The Consensus Panel concluded that osteoporosis was a major public health problem requiring additional research on the biology of human bone, defining individuals at risk, and developing safe, effective, low-cost strategies for fracture prevention (10). The panel recommended studies to develop accurate, safe, inexpensive methods for determining the level of risk for osteoporosis in an individual, to establish early diagnosis, and to assess the clinical causes of the disease (10).

In February of 1987, as a followup to the Consensus Development Conference, NIH sponsored a scientific workshop on research directions in osteoporosis (58). Quantitative computed tomography, SPA, and DPA were discussed and listed as methods that offered a dramatic improvement over previously available methods of determining BMD. The group reported that measurements of bone mass or change in bone mass in peripheral sites do not accurately reflect bone mass or change at axial sites (spine or hip), which are areas of greater interest. Consequently, measurements at any one site do not allow prediction of mass or change in mass at another site in an individual (58).

According to the Food and Drug Administration (FDA), the laboratory presently using the RA technique to read radiographs is providing a service, and, as such, is not actively regulated by the FDA.

In June 1984, through its Clinical Efficacy Assessment Project, The American College of Physicians published a policy statement on radiologic methods to evaluate BMC (6). The College concluded that all methods of BMC measurements result in significant overlap between diseased and normal populations. They stated that the ultimate benefit of early diagnosis of metabolic bone disease will depend on the clear establishment of safe and effective treatment. The College believes that measurements of BMC have greater utility in following the course of disease process or assessing the effect of therapy than in establishing a diagnosis. According to the College, none of the available techniques, including RA, accurately predict the tendency to fracture (6).

The Orthopedic Research Society strongly supports continued research in the development of noninvasive techniques for understanding metabolic bone disease. The Society suggested that research examine the precision, accuracy, sensitivitiy, cost, availability, and relevance to underlying metabolic disease of each of the techniques currently under study. The society also suggested holding a workshop directed at the understanding of the surveillance of bone disease.

It is the opinion of the Society of Nuclear Medicine that bone mineral density studies should become part of the workup of patients with osteoporosis and that DPA is the technique of choice at this time. According to the Society, other methods performed on appendicular bone are of little value in patients with osteoporosis. However, they may have some application in patients with renal bone disease.

A response from the American College of Nuclear Physicians stated that osteoporosis can be detected at its earliest stages by DPA measurements of the vertebral spine. According to the College, in order postpone or prevent the problems of insidious progressive osteoporosis, early detection and screening by bone mineral analysis of the

lumbar spine by DPA is critical. The College finds DPA of the spine far superior to appendicular measurements in detecting most cases of early osteoporosis. They suggest, however, that in older patients with significant degenerative spine disease, appendicular measurements may be helpful in management on an individual basis.

SUMMARY

Radiographic absortiometry is a noninvasive radiologic technique involving a computer-assisted densitometric measurement of the x-ray image of bone. Mineral density analyses are based on phalangeal scans of pairs of lightly exposed radiographs with an aluminum alloy reference wedge included in the image field. After a computer-controlled optical densitometer scans the x-ray image with a light beam, the system is designed to compare the findings with normal values of phalangeal bone size and BMD determined from age- and sex-matched controls. In RA, bone mineral mass is determined and expressed as BMD (mineral concentration) by accounting for bone size (bone image area). Using currently available equipment, the technique can achieve a precision of 2-4 percent with a radiation dose of 10-100 mrad.

The measurement of bone mass is an important tool in the study of metabolic bone diseases, such as osteoporosis and renal osteodystrophy. While RA is capable of measuring BMD and has advanced our knowledge of bone disease in general, its impact on the management of the individual patient is equivocal. Although the technology to measure bone mass noninvasively with RA is currently available, the ability of such measurements at the phalanges to predict individuals at risk for subsequently developing fractures of the spine and hip (screening) has not yet been shown.

Studies with RA that attempted to find a specific level of bone density that distinguished patients with vertebral osteoporosis have been largely unsuccessful. Other studies with RA measurements have reported statistically significant correlations

between bone density of the phalanges and that of total body calcium. However, a large scatter in the data precludes a reliable prediction of bone mineral from one site based on measurements at another site in an individual.

Other clinical applications proposed for the RA technique are to monitor rates of bone loss and to determine the effectiveness of treatment. A high degree of precision in the bone mass measurement is necessary for repeated measurements of small degrees of change, and such precision is difficult to attain. Presently, the suitability of the phalangeal site for monitoring changes in bone loss is questionable.

Investigators have not established the need or appropriateness of RA measurements in the management of renal osteodystrophy for ESRD patients. Radiographic absorptiometry needs to undergo further clinical investigation before it can be recommended for general clinical use.

With regard to its regulatory status, the Food and Drug Administration stated that the laboratory presently using the RA technique to read radiographs is providing a service, and as such is not actively regulated by the FDA.

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[FR Doc. 88-20408 Filed 9-7-88; 8:45 am]
BILLING CODE 4120-01-C